DEPARTMENT OF HEALTH AND HUMAN SERVICES

ADVISORY COMMITTEE ON BLOOD SAFETY AND AVAILABILITY

Eighteenth Meeting

"Prioritizing Decisions in Transfusion Medicine:

Transfusion Transmissible Diseases."

8:28 a.m.

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P A R T I C I P A N T S

Committee Members

Larry Allen
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Richard Davey, M.D.
Ronald Gilcher, M.D.
Edward D. Gomperts, M.D.
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Lola Lopes, Ph.D.
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John Walsh

Non-Voting Government Representatives

Mary E. Chamberland, M.D.
Jay Epstein, M.D.
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Consultants to the Committee

Christopher Healey, J.D.

Captain Lawrence McMurtry

C O N T E N T S

P R O C E E D I N G S

DR. BRECHER: Welcome to the second day of the Advisory Committee on Blood Safety and Availability. We have a couple of business items we wanted to take care of. One, I wanted to remind people that while we have presentations this morning, there will be a Committee discussion this afternoon, and we're discussing resolutions, and I don't think that we will take the entire afternoon. My guess is we'll be out by 4:00 at the latest, if not sooner, unless I hear any objections.

The second point is there was a question of us discussing smallpox and the ramifications for the blood supply. It was pointed out that we did not really have any speakers prepared to discuss this subject and that is a very important subject, and that really deserves the attention of this Committee, and it has been suggested to me that we postpone that discussion and actually reconvene the Committee on a one-day basis sometime in a couple of weeks for a one-day meeting to really address the issue of smallpox vaccination and its impact on the blood supply. And so if the Committee would agree to that, I would propose that that's what we do.

We can, perhaps, at the same time could also have one or two presentations on whatever happened to the HCV lookback and bring closure to that item as well. So

all of those of the Committee who are in favor of putting off the smallpox discussion until a few weeks?

[Show of hands.]

DR. BRECHER: That motion carries.

CAPTAIN McMURTRY: I want to do one more housekeeping item just for the record. He's not here now, but I want the record to show that Larry Allen did come in yesterday. I had him as absent.

DR. BRECHER: This morning we're going to move away from viruses, which we basically concentrated on yesterday. I had said we would start on time, if not a few minutes earlier, and given the weather outside, I thought this would be an appropriate way to start here.

I stole this from Sunny Dzek, who presented it at an NHLBI Transfusion Medicine Hemostasis Clinical Network Steering Committee meeting last week, and I thought it was quite appropriate.

I think there's only one other person in the room who was there.

[Laughter.]

DR. BRECHER: We have to watch this closely here.

[Laughter.]

DR. BRECHER: If nothing else, it breaks the ice. Now, for those of you who weren't paying attention, watch his foot.

[Laughter.]

DR. BRECHER: Now, if that wasn't bad enough, this is called the evil penguin returns.

[Laughter.]

DR. BRECHER: So those two Sunny presented at the meeting, but I was really puzzled by all of this, and so I did a little searching on the web that night, and this apparently is the original footage from which the other two were digitally altered.

[Laughter.]

DR. BRECHER: So that second penguin was never really there. So seeing is not necessarily believing, and sometimes appearances are deceiving.

So let's talk about bacteria, and I fudged a lot bit. That's actually a Chagas organism flowing through the bloodstream there, but we're going to talk about bacteria, and I'm going to talk about red-cell contamination and then platelet contamination. I'm going to go zipping through the red-cell contamination because that's not really where the problem is.

But these are the kind of headlines we, as blood bankers, really don't like seeing, but it's a very important problem. You know, how safe is our blood supply? And for those of you who can't see how important this is, it even overshadowed the OJ Simpson story up here. So this is really important, and it began by

talking about this man, Rollin Tobin, who was the public safety director for Southfield, Michigan, who was undergoing a total joint replacement, had donated three autologous units, but needed two allogeneic units, red cells, in the operating room.

To make a long story short, he became septic and died about 24 hours after his surgery from overwhelming Yersinia enterocolitica sepsis. It was a complicated story, and I'm not going to go too much into it, but this particular case went to a jury trial. Many times these cases lead to a lawsuit, but you never hear about them or you never can talk about them because they tend to be settled out of court. This particular one went to court, and the jury awarded the family $5.6 million in a wrongful death suit. So these can be very expensive lawsuits.

Now, it's not just in the U.S. that this happens. We think of the U.S. as being a very litigious country, but I took this one off the BBC website from about almost a year ago, where another red-cell contamination, where the family was awarded 300,000 pounds for brain damage that resulted from a patient becoming septic. So these cases can be quite expensive for a hospital if they do occur.

Now, with red-cell contamination, the two major organisms tend to be Yersinia enterocolitica and serratia

liquifaciens. The reason is that these two enterobacteriaceae can grow quite well in the cold, in the refrigerator. They have endotoxin, and when you get a unit that is contaminated, generally the bottom falls out clinically--hypotension.

And then for Yersinia, this is a summary of 20 cases that were put together by the CDC, a couple major points. Sixty-percent of people who received Yersinia-contaminated unit died. So roughly half the people will die, and they tend to die within 24 hours.

If you have DIC, seven patients had DIC, including Rollin Tobin, six of these seven died. So if you're going to DIC, it's a very bad prognosis.

The incidence for red-cell contamination for Yersinia, there's some regional variability. The highest numbers have been reported from New Zealand, where they had an incidence of 1 in 65,000, and again roughly half of the cases resulted in a fatality. No one knows why there was such a high incidence in New Zealand back when this was reported. The numbers seems to have decreased in more recent years.

In the United States and Canada, it's estimated that the chance of dying from a red-cell contaminated unit is less than one in a million and may be on the order of one in nine million. Interestingly, I've been talking to Matt Ardvino at the CDC. There has not been a

fatality from Yersinia in over a year. We're not quite sure why that is, but it may have, we've just been speculating, it may have something to do with the leukoreduction of red cells in this country that you were actually filtering out the Yersinia pre-source leukoreduction.

Several years ago we did experiments on red cell-contaminated units, and we found that over time the units turned darker, and you could actually see the dark color extending down the tubing until you get to the-- it's a little hard to see in the slide, I'm afraid--but I'll show it to you better.

Here you see the dark blood coming from the bag, and then you get into the segmented tubings where they're not dark, and this is a sterile tubing up here. The reason they become dark is that as the organisms grow in the red cells, the oxygen drops to zero. So we have two units that have Yersinia growing in them here, as opposed to sterile units, where the PO2 in the units started around 40 sort of venous blood and very slowly creep up to the PO2 of room air.

We talk about these plastic bags breathing, but they breathe very slowly. In addition, there is some hemolysis of these units, and cell-free hemoglobin is darker than cellular hemoglobin. I know there have been

some scattered reports suggesting there may be some methemoglobin
formation inducing this as well.

Now, here's a particularly striking example. See the dark color of this unit compared to the segmented tubing here. Of course, when the PO2 drops, the hemoglobin becomes completely desaturated, and so it is darker.

This is actually a unit that was hung in a hospital. I got this picture from the CDC, and this is actually serratia liquifaciens. It gives you a very dramatic color change. We've grown this in our lab, and the units look just like this. In this case, with serratia, homolysis precedes a drop in the PO2. So the hemolyzed unit is bad news.

Now, the other interesting thing is, CDC, about a year ago, published seven case studies of serratia liquifaciens. Two of those cases discussed that once they figured out there was a contaminated red cell unit, they said whatever happened to the recipient of the platelet that was made from that whole blood donation? And so they looked back.

In one case, the patient had died of overwhelming sepsis, and of course the organism that grew was serratia liquifaciens from that patient, but they had not put together that it had come from the platelet, and

this is a very common story. The other one was sick and had a bacteremia with serratia, but fortunately did survive.

So this is a very common thread with platelet reactions is that they tend not to be recognized, and it's sort of, through serendipity that you figure it out that it happened.

Now, some of this material was presented yesterday. I'll go through it, but this one approach to looking at the math. There are about four million platelet bags transfused in the U.S. every year; roughly, one million apheresis platelets, single-donor apheresis bags, and three million random donor or whole blood-derived platelet concentrates.

The contamination rate, based on a number of studies, principally using aerobic culture techniques, suggest that the rate is about one in a thousand to one in two thousand bags are bacterially contaminated. That means that in the U.S. we are transfusing 2,000 to 4,000 bacterially contaminated bags.

Now, the data in the literature suggest that maybe a quarter to a sixth will result in clinical sepsis of varying severity, but that works out to roughly 333 to 1,000 cases per year, of which perhaps a fifth to a third result in fatalities. So 67 to 333 deaths per year or a

fatality rate of 1 in 60,000 units transfused to 1 in 120,000 transfused.

Now, are these numbers real? Data from hospitals that have closely looked for these reactions, such as Johns Hopkins, which has had a long interest in bacterial contamination platelets, Paul Ness published a paper in the past year where he reported that the risk of dying from a pool of random platelets 1 in 17,000 in his institution, out of a pool with six. So you'd have to multiply it times six to get the unit number. But for an apheresis pack, it was 1 in 61,000. So we're right in this range.

And, of course, he only knows about the cases that were reported back to him. So he may have missed a few cases. So I think that this estimate is a reasonably good estimate for what's happening in this country.

Similar numbers have been reported from the University Hospital of Cleveland, another institution that has really concentrated on bacterial contamination of blood products. So there's a heightened recognition of these reactions in those two institutions.

Now, I think this is a third or maybe the fourth time we've seen a figure like this. We've done a great job, both industry and in the blood centers, in reducing the risk of HIV, HBV, and HCV over the years per unit.

Actually, this was in the handout of the article that was in the Lancet last week.

But for the risk of bacterial contamination per bag, we have not done as good a job. The risk has remained approximately 1 in 1,000 to 1 in 2,000 for years. Now, the one thing we have done is there has been a push in this country to switch to apheresis platelets, and I think roughly two-thirds of doses being handed out in this country now are apheresis platelets, but the risk per bag has not really changed.

Now, there are a variety of organisms that contaminate platelets, unlike what you see with red cells. The difference here is that platelets have to be stored at room temperature, and so they are a good growth media. If you were to just look at the organisms that grow from platelet bags, about two-thirds of them tend to be gram-positive organisms, like Staph epi and Bacillus cereus, so skin saprophytes.

However, if you look at what actually kills people in the U.S., and this is data from the FDA, roughly, 23 years, 51 fatalities reported to the FDA, it tends to be the gram negatives that kill people more than the gram positives, like Klebsiella, Proteus mirabilis, E.coli, Enterobacter, Pseudomonas Salmonella and Serratia. Most of these are enterobacteriaceae, except

for Pseudomonas here. So it's the gram negatives or the organisms that we need to worry the most about.

Unfortunately, the patients who tend to receive platelets often are immunosuppressed. More than half of all platelets that are transfused in this country tend to go to heme oncology patients or bone marrow transplant patients, and they are not in a good position to fight off bacteria.

The gram positives, probably many people who are immunocompetent might be able to handle gram negatives. I think if you get a unit that's heavily contaminated with gram negatives, it doesn't matter whether you're immunosuppressive or not, you are probably going to die.

A variety of strategies have been suggested to address the problem of bacteria contamination. Growth inhibition, the question has been raised about what if we just put some antibiotics in every bag of platelets? It probably would solve the problem, but it would present new problems, and there's been a great reluctance to, one, trade a relatively rare reaction, fatality from bacterially contaminated platelet, for idiosyncratic drug reaction.

And, two, we would be spreading a little bit antibiotics all over the hospital, and we would be selecting for antibiotic-resistant bacteria, and so this has not really been considered a real possibility.

Temperature, a lot of research has gone into trying to refrigerate platelets, but to date this has not worked. Bacterial avoidance, let's try to keep the bacteria out of the bag. I'll come back and talk about that in just a bit. Bacterial detection we'll talk about, and I'll just briefly mention elimination, but we're going to have a whole talk on pathogen reduction later this morning so I'll stay away from that.

What about just trying to get a safer bag of platelets, less chance that there will be bacteria in the bag. Bacteria comes from two sources. It comes from the skin or it comes from a unit who has, it's come from a donor who is an asymptomatic bacteremia. Most of the gram negatives are from donors of asymptomatic bacteremias.

Recognizing this, the group at Johns Hopkins made a conscious decision back in 1986 to try to move toward an all apheresis blood supply. So, in 1986, roughly, 52 percent of their platelets were apheresis platelets, and 48 percent were pools of random donor platelets, so a six-pack.

By 1998, they had gotten to the point where 99.4 percent of all platelet doses being transfused at Johns Hopkins were apheresis platelets. During this time, their reaction rate, where people who actually had clinical signs and symptoms from these transfusions

related to bacteria went from roughly 1 in 5,000 transfusions to 1 in 15,000 transfusions.

The difference in risk between these two products was between five to sixfold, as you would expect from a six-pack, compared to one bag. And so there were many institutions that have used this strategy. In fact, to be honest, when a patient needs a platelet transfusion, and they receive an informed consent for transfusion, how informed is it really?

Do you really say, well, we can give you a six-pack of random donor platelets for X number of dollars that's going to cost the hospital, it's cheaper, but it has six times the risk of bacteria or we can give you a single-donor apheresis platelet that's going to cost the hospital a few dollars more, but has one-sixth the risk of bacteria. That question never gets asked.

There have been some data from Europe that have advocated the diversion of the initial couple mLs of collection. It's thought that this is the most contaminated from the skin and that there may be a skin plug that comes off the needle. There have been some large studies from Europe that support this.

This study from France, they looked at, roughly, 3,400 collections, where they looked at the first 15 mLs of blood, where 76 units were contaminated, and then they looked at the second 15 mLs, where only 21 were

contaminated. So it wouldn't take care of the entire problem, but it would cut down on some of the skin contaminants coming into the bag.

Similarly, a larger study from the Netherlands, 18,000 collections, .35 percent were contaminated. They diverted the first 10 mLs, and the contamination rate dropped to .21 percent. There is some move in this country to go in this direction. It has been discussed at the BPAC. It was not thought that the data was strong enough to warrant that this be a requirement, but people are moving in this direction. It's a small step or, as my colleague, Ros Yom Tovian, likes to say, we shouldn't be diverted by diversion. It will do something, but it's not a very good solution.

What about skin disinfection? This is a study from Canada, from Indie Goldman. It's sort of a busy slide. Basically, they did touch preps on the antecubital fossa after the skin had been prepared by a variety of skin disinfectants, and they looked at how many colonies were present afterwards.

The message here is that when we cleanse the skin, we do not make the skin sterile. All we are really doing is reducing the bacterial load on the skin. There's a suggestion in this paper and in another study from London that the use of tincture of iodine is

superior to the povidone iodine, which tends to be the standard of care in this country.

Interestingly, another thing that came out of this study was they looked at green soap and isopropyl alcohol. Green soap was commonly used in this country to prepare the antecubital fossa of donors who were allergic to iodine. In one-third of the cases in this study, there were more bacteria after the green soap than before the green soap. All they did was stir things up, and so there has been a move, particularly from the AABB, to say green soap is not an acceptable alternative.

There is another skin prep, chlorhexidine, which does a reasonably nice job, and actually the new version of the AABB standards that will be coming out this year will specifically address this, and green soap was dropped from the AABB technical manual in the last addition.

When you're talking about platelet contamination, timing is a major issue. Data from Mo Blajchman from Canada, they looked at 16,000 random platelets on the day of collection, which they called Day One. A lot of people would have called that Day Zero, but we'll let him get away with it, where they found four positives, a contamination rate of .02 percent.

They came back two days later. There were still 10,000 of these bags in their inventory. Now, they had a

culture-positive rate of 7. So the rate went up to .07 percent, so it more than tripled. The message here is that if you want to find the bacteria, a sample from the bag, right after you've collected it, is not going to detect most of the cases. You have to allow some time for the bacteria to proliferate so that a random small sample from the bag will have bacteria in it that you can actually identify.

These are growth curves for several of the most common, contaminating organisms, and clinically significant organisms from my lab at UNC, where we spiked in at low concentrations on Day Zero, usually 10 to 50 CFUs per mL, colony forming units bugs per mL. What you can see from these drawings, and this is Bacillus, Pseudomonas, Klebsiella and Serratia, is that usually by Day One or Two, you have significant amounts of bacteria-- these are log curves--and that generally you reach a plateau by Day Three or Four.

With Bacillus, often you're on plateau growth by one day, 24 hours, and probably a Day Three- or Four-day-old-platelet and is probably no more dangerous than a Day Six or Seven platelet, in terms of bacteria. If they're going to grow, these things tend to grow early.

Now, there is one organism that I don't think you can say that about, and that's Staph epi. That tends to be a slow grower. There's some data to suggest that

the initial concentration has an effect on the lag phase and that Staph epi may take quite a while to grow.

This is just to remind me to emphasize that you can't test the whole unit. I guess I have to change the slide again because we're coming to the end of January 2003. You can see it's yellow, it's a platelet.

Detection techniques. A variety of both high-tech and low-tech approaches have been described in the literature. I've been fortunate, many of these technologies have played through my laboratory over the years, and I'm just going to concentrate on a couple of the technologies that have actually made it out into the world, that have actually been used.

One is bacterial staining. It doesn't matter whether you use a gram stain or a Wright stain. Some people prefer a Wright stain because the labs have these automated Wright stainers in the hematology lab. You put a little slide on a little conveyor belt, and it goes and out comes a perfectly stained slide at the other end, and we don't care whether it's a gram negative or a gram positive. We just want to see that there's bacteria there.

The bottom line is that with a gram or a Wright stain, you pick up at around 10 to the 6, maybe 10 to the 7 CFUs per mL, so it's not particularly sensitive. You could do acridine orange, where you can make the

bacteria, the DNA, glow back at you, but it requires a fluorescent microscope, and it only gets you about one log better, so not all that great, but it has been used sporadically, particularly at the University Hospital of Cleveland, where they were able to interdict several bacterially contaminated--heavily contaminated--units.

Some people have advocated using dipsticks, urine dipsticks, looking at the drop in pH, where it would turn orange, or the drop in glucose. As the bacteria grow, they consume the glucose in the bags, and this is a slide from one of my papers on transfusion. Here, we've got Klebs pneumoniae and Staph aureus, and you can see the dipstick is blue, blue here from glucose, or if you can't see it, use your imagination, and the pH is orange.

Now, both of these units were Day Three after contamination, contaminated on Day Zero, and the organisms were at 10 to the 7 CFUs per mL. However, we would have missed this one, Serratia, where the glucose was not dropped sufficiently to turn it blue, and the pH was not orange because it was only at 10 to the 3rd CFUs per mL. So sort of across-the-board dipsticks pick up about 10 to the 7 CFUs per mL, about comparable to a gram stain. Now, they're somewhat easier to use, and they're relative cheap, pennies a dipstick.

There's a recent report from M.D. Anderson, where they screened 3,000 random platelets, and they found two that were contaminated with bacillus cereus using this dipstick technology, and they were able to interdict those units.

Now, to do that, they also found 28 units that did not pass the dipstick. You may say, well, it's specificity isn't very good, but you could come back and say, well, if the pH was really 6.5 or there was no glucose left in the bag, maybe those platelets weren't any good any way.

Most of the interest has concentrated in recent months on the two bacterial culture methods that have recently been approved by the FDA.

One is the bioMerieux BacT/ALERT microbial detection system. This is an automated liquid detection system, where you put your sample and question into one of these bottles, load them onto these machines, and over time, as the bacteria grow, they generate CO2, and the CO2 causes a color change in this colorimetric sensor at the bottom of the bottle.

There's a very similar system out by Becton Dickinson called the BacTec system, but it is not approved for platelets in this country, where the color change goes from green to yellow, and roughly every 10 minutes every bottle is scanned. There's a little light

that reflects off here, and it goes to a sensor. There's a computer hooked to the system where it looks at both the absolute color, but also what is the rate of change of the color so that it picks up these units before the human eye would pick them up.

In my lab, we've looked at 14 or so different organisms in platelets with these machines using all of the types of bottles that they have. For the vast majority of them, we would have picked, at 10 CFUs per mL or lower--some of our units were at 1 CFU per mL--we would have picked up most of these bacteria, roughly, at 12 to 14 hours. In some cases, it would have taken 24 hours, with the notable exception of propionibacteria acnes, which is an anaerobic organism, which actually takes days, but the clinical significance of propionibacteria acnes is not clear and probably has little clinical significance.

The other system that was recently approved, and both of these systems, I should note, are approved for in-run quality control. They are not release control, so you cannot make a claim of sterility if you use these two techniques.

There's a system from Pall, their Bacterial Detection System or BDS, and what happens here is you push over about 6 mLs of your platelet solution in question, and it goes through a filter. It wouldn't be a

Pall product unless it had a filter in it. I know the Pall guys are here.

The filter filters out white cells and platelets, but lets bacteria pass. And sort of across the board, about 50 percent of bacteria cross this filter, and so then you have 2 mLs that make it into this little side pouch, and there's a little SPS tablet in here which inhibits the inhibitors of bacterial growth, and so it allows bacteria to grow better in this little bag.

You clip off this little bag, you put it in a 35-degree incubator for 24 to 30 hours, and then you measure the PO2 of the headspace gas of this bag to see if it's below a cutoff. As the bacteria grow, they will consume oxygen, similar to the diagrams I showed you for Yersinia and red cells before.

Now, I'm not going to say much about pathogen activation--I'll leave that for Steve Wagner--other than to say Cerus, which is the one that has the most studies out there, is very good at inactivating in five logs a variety of bacteria, although it may have some trouble with spore-forming organisms. If it forms a spore, the chemicals may not be able to get into the spore.

Now, here's that crystal ball somebody was talking about yesterday. What's the future? The future tends to lie in the past, and referring back to our IOM

report which we went over yesterday, and I think Lola mentioned this, Recommendation 6, this is my favorite one in the report: The perfect should not be the enemy of the good. Implementation of partial solutions that have little risk of causing harm should be encouraged.

I think that's where we are with bacteria. We don't a perfect solution right now, but we have a lot of partial solutions that would take us most of the way.

The FDA has sponsored three workshops that dealt with bacteria over the last seven years. This is a summary, summary comments made by Ed Snyder in the '99 meeting. I have Ed's permission to use this.

He concluded that the imperative is to act, so you don't have to explain yourself on Nightline and regulation is necessary to achieve the goal. Nothing says I care like a page of 483s--483s are the citation forms left from the FDA. So if you get dinged, you do something about it.

When all else fails, do something. Give us a mandate, and we'll do the rest. I think that's sort of where we're at. Unless blood banks are told to do something by some higher organism, be it FDA, AABB, CAP or some organism, the hospital administrators are not going to let us do this.

Following the meeting last August on pathogen reduction, five of the speakers and moderators from the

meeting got together, and we wrote this letter which was published as an open letter to the blood banking community. In this letter, we basically said:

"It's our feeling that pathogen reduction won't be here in the short term. Nevertheless, bacteria contamination of platelets is a major problem in blood banking, and we feel that the implementation of detection strategies should be implemented now."

This got a lot of coverage. It was put up on a lot of electronic sites going out in the blood bank newspapers. Interesting results. In fact, there was one comment posted on the California Blood Bank Society page that accused us of moral blackmail, and I think it's only moral blackmail if we're moral.

[Laughter.]

DR. BRECHER: Now, AABB has been talking about this, and they did publish for comment their proposed 20-second AABB standard, which was the new standard 5.1.5.1, that the Blood Bank and Transfusion Service shall have a method to test for bacteria contamination of all platelet components.

I have to say that I'm aware that the wording has been changed. The final wording is not approved yet, and so it's not clear exactly what will happen with the AABB, but this may be the mandate for bacterial testing of platelets that the country needs.

The other thing is we need to recognize that in '82 the platelets were extended from three to five days; in '83, from five to seven days, because of good data function and survival of these platelets. But in '86, because of reports of bacterially contaminated Day Six and Day Seven platelets, it was rolled back to five days. There is now a lot of interest in going back to seven-day platelets. If anything, the platelets are better now than they were back in 1986. The plastics are better, the white cells are out of the bag, the platelets survive better.

There have been a variety of reports from Europe that have coupled culture to the extension of the platelets in Europe from Denmark, the Netherlands, Yugoslavia, United Kingdom. In fact, several countries, such as Norway and Sweden, are routinely culturing all of their platelets.

Several institutions in other countries, including HemaQuebec, but in this country, Dartmouth, the University of North Carolina have been culturing their platelets.

Finally, we heard from Jim AuBuchon yesterday, and Jim is probably the king of cost-effectiveness studies in this country. He's published a lot of major cost-effectiveness studies, and it tends to be that every time he says something is not cost-effective, p24

testing, NAT or whatever, he says it's not cost-effective, we go ahead and do it anyway; is that a fair statement?

He hasn't published a paper, but he had an abstract back in '99, and basically he said, hey, this is a cost-effective strategy. If we culture and get an extra two days of outdates on our platelets, it will easily pay for all of the culturing in this country, and so this could be a win-win for everybody--safer blood at less cost, as unbelievable as that may sound.

Also, there have been data from other countries that also support this stuff. They actually save money by culturing and extending an extra two days on the shelf life.

Finally, I want to end with this quote, which is actually how we ended this Lancet paper about looking to the future that was published last week and was distributed to the committee members yesterday.

"Actions are right to the degree that they tend to promote the greatest good for the greatest number. By John Stuart Mill."

Now I can take some questions.

Celso?

DR. BIANCO: Mark, thanks for a very nice review. I have two questions for you. The first one, if we went the other way around and looked at what

contribution, that is, probably a lot of things will be implemented in the next year or so. It's the better skin prep, more attention to the skin prep, the diversion bag, and the culture. How much each one of those procedures will contribute to reduce the risk of bacterial contamination--ballpark? I know it's difficult.

DR. BRECHER: I think the skin prep and the diversion have the potential to cut down on the gram-positive contamination, but I don't think it's going to be more than half of the gram positives.

What worries me more in that two-thirds of the debts are from gram negatives, and neither diversion or the skin prep are going to impact on the gram-negative organisms. So the only way we're going to get to where the real fatalities are is with a detection system or with an inactivation system.

DR. BIANCO: The second issue is surprisingly both systems that we have now for bacterial detection were approved for quality control, not for unit release. That, in the short term, certainly helps in the sense of making those systems available on a wide scale, but in the long term, and I'm giving my personal opinion, I think that the approach was detrimental because it doesn't allow us to really say that the unit has a lower bacterial load because the culture was negative or something like that.

It interferes with our extension of the seven-day platelet and also discourages the manufacturers from pursuing full clinical trials and licensure of their tests in a format that would be really compatible with life.

I wonder if you could give us your opinion about that and what kind of quality control we could do, in a limited number of units, that could reflect the overall process and give us more certainty or more--

DR. BRECHER: The problem, as I see it, what we would require for release control would be a study of the magnitude of the NAT testing implementation. It would be an IND that would have to go across the country because the incidence is so low, and so it's almost impossible to prove true clinical efficacy on a large scale that I think that the FDA might want. I don't want to speak for the FDA.

Jay, do you want to say something about that?

DR. EPSTEIN: Yes. The problem, in a nutshell, is that to validate the actual benefit of the up-front test, you need a follow-up culture at either the time of issue or outdate on the very unit that you cultured either on Day One or Day Two in order to validate the sensitivity of that procedure, and the companies have not stepped forward to do that study, nor has it been done otherwise in an investigator-sponsored study.

So we're left not knowing what the up-front culture really does. We know it sometimes detects contamination, and if it's done "in real time," which means while you sell the unit in inventory, of course, there's an obvious benefit pulling that unit, but we really just don't now. Was that 50 percent of the units, 75 percent of the units?

So, in order to be able to make a statement that the up-front culture, done in a certain way, has a certain predictive value for a culture-negative product at issue, you have to do a more comprehensive study. Now, there are two barriers; one is the added cost of the follow-up culture, and the other is the need for large numbers.

The problem of large numbers is, in fact, easily remedied if any large part of the system does move to a routine quality control culture. You're going to be doing it. The question then is how do you fund the endpoint culture to validate the up-front culture.

I agree that it makes perfect sense to link this to extension of dating. The bug bear there is that we need, just as the platelet bags, oxygenation, et cetera, have improved, we need the validation data that we still have a quality platelet by today's standards. In other words, what might have been accepted in '86 for a five-day platelet may no longer be acceptable today, and we

want to know that the seven-day platelet is, in fact, acceptable.

What we do know is that the platelets are deteriorating progressively on storage, and so it's a bit of a question of what's the belt line. But these issues have to be put together. Well, there are one of two ways to get the correct study funded, either to have antecedent data that you can extend data and therefore funded by extension of dating or to have supplemental funding so that you can study them at the same time.

I mean, neither of those approaches is infeasible, but the parties that need to step forward have not done so. So the Agency, you see, was left with a very difficult problem. We had culture systems that were validated to sometimes detect bacteria. Their actual clinical value was never measured, and the conditions of use were therefore not validated in any predictive way. So the most they could say is that, you know, if you do this, you'll sometimes detect bacteria.

Well, if you approve them for quality control, you eliminate the issue of whether it's being done real time. A quality control culture to monitor the frequency of contamination to ensure that you have a system operating under control with the expectation that the contamination rate is of the order of 1,000 to 2,000, as is the current state-of-the-art, is feasible whether

you're doing an online culture or an offline culture. You could do quality control simply by sampling at issue or outday. Indeed, you could do it solely at outday, and the time taken to do to the culture and report the culture does not have to be commensurate with the shelf life of the product.

So the standard for approving it for quality control was a lot lower than a logical standard to approve it as a release test; in other words, a test with a certain predictive value of a nonculturable unit at issue.

We brought this whole matter to the Advisory Committee. There will be a summary later today of the discussion at BPAC, but the Advisory Committee agreed with the FDA that what we had described as the proper design of a study to validate a claim for a release test is scientifically appropriate.

Now, of course, we have an open mind, if people have a better idea. But the problem, as I see it, is that there has not been the will, you know, expressed through a funding mechanism, to simply do the appropriate study, but it's nothing arcane. It just requires a follow-up culture.

DR. BRECHER: Let me just comment on that. There have been two centers that have been running pilot studies like that, but they're small. Dartmouth and UNC

have done this on a small scale. Dartmouth has done about 4,000 apheresis platelets, and UNC has done 2,500, roughly, to date.

At least we can say that the contamination rate that we see on the early cultures are similar to what's been reported in the literature. At least at UNC we have not seen any that we didn't pick up on a Day Two culture, and we've, actually, in 2,500, we stopped three Staph epi units from being transfused.

That said, when you do the statistics, and I've had several statisticians look at this and none of them seem to agree, but the message seems to be that you need about 120,000 platelets to validate this, to show that it really is statistical.

If you're only going to do the outdated platelets, Day Seven, and roughly 10 percent of platelets outdate in this country, we're talking about basically enrolling about a million platelets into the study and only picking up the Day Sevens.

Now, there may be some give, and maybe we can do issue platelets, instead of just Day Seven, but it is a large study, and I actually have had some discussions with the Red Cross, and they are interested in, at least initially, they said that they would be interested in reculturing their outdated platelets, and so maybe within a couple of years we can generate this data.

Is that safe enough?

DR. EPSTEIN: Well, I'm not going to comment on the study designs and the data submitted. I can't do that publicly.

DR. BRECHER: Yes, well, this data is not submitted.

DR. EPSTEIN: All I can say is that what the Agency has seen to date is not sufficient and that there is a problem of numbers, but as I say, if the system moves toward 100-percent quality control testing, you have the infrastructure to very rapidly do a large study if there's a way to fund the follow-up culture.

DR. BRECHER: Celso?

DR. BIANCO: My problem, and I think that it's very much the purview of this committee, instead of BPAC or the FDA, is that the fact that those companies were licensed or had their systems approved for quality control, those companies have no encouragement to go in and invest into the next step. So my question to Mark and to the Committee is how can we encourage them? Because I think that our goal is to have 100-percent bacterial detection.

DR. BRECHER: One strategy we thought was going to be a good one was to take us to the new transfusion medicine, hemostasis clinical network, but when we ran the numbers the cost just exceeded the money that was

available in that network, and so that project was put on hold. I don't know where the money is going to come from, unless the blood centers just agree to do it because, in the long run, it will benefit them.

DR. DAVEY: Mark, I think we can all agree that moving to single-donor platelets is a good idea from whole blood-derived platelets, but that's going to be hard to do, at least in the near term.

What do you think about the proposal that's been floated to pool whole blood-derived platelets at the blood center and then test the pool, similar to what's been done in Europe, to some extent.

And perhaps a question for Jay, what would be needed to approve such a technology?

DR. BRECHER: I think logically it makes a lot of sense. Europe has been doing this for decades. My guess is that it would require an IND from the FDA, but I think it's feasible. I think we should move ahead. Someone should do a big study like that.

Keith?

DR. HOOTS: In terms of the sensitivity, I mean, compared to culture, some of these techniques, are they in Day One or Day Two, how many bacteria per mL are they capable of detecting, did you say?

DR. BRECHER: Well, there are papers out on the bioMerieux system that suggests that they can detect down

to one or even less CFUs per mL. So let's just call it at least one CFU per mL. The abstract presentations on the Pall BDS suggest that they pick up down to 10 to 100 CFUs per mL.

DR. HOOTS: Just in terms of at the far end, since you made a great point about incremental things until you can solve the whole problem, in terms of practice, it's been my experience that a lot of times, and probably it applies most to immunosuppressed patients, BMTs, and leukemias and that sort of thing, that when blood products are ordered and are hanging or getting ready to be hung, that they will just come to the floor, and they'll get hung.

If the patient happens to be on antibiotics, say, because they have leukemia, and they've had neutropenia, they'll delay the antibiotics to get the blood hung, particularly if they only have limited access. I just wonder if just something as simple as saying, you know, make sure that if they're on antibiotics, they get their antibiotics, and then hang the blood or the platelets, particularly the platelets, if they happen to have a small contaminated unit, as opposed to something that you might see causing a fatal transfusion bacterial contamination. It might buy them some time.

DR. BRECHER: It might, but, clearly, there have been fatalities in people who were receiving around-the-clock antibiotics, and I think it's going to depend on the organism, the sensitivity of that antibiotic, and if you're getting a big flush of endotoxin, it doesn't matter what antibiotic you're on.

John?

DR. PENNER: I think this is the body that should be recommending a program of study and funding for it. If it's apparent at this point that we're running into a question of having something done, and if it needs to be accomplished, we need to get behind it with some form of resolution, and I don't see why this can't be done, even today to provide at least some prodding for proceeding in that direction.

Incidently, the unit of blood to protect Michigan came from Wisconsin, for the Detroit case, and it was a dairy farmer who was a carrier for Yersinia.

DR. BRECHER: I tend to agree with that. I think this is the right body to make a recommendation. And one of the things, when we went back through the grid, that I think we've been successful is identifying areas that needed to be funded and that have subsequently been funded.

Now, I'm in a difficult position, being Chair of this Committee and having a real interest in this

bacteria, so I'm going to try to step back and just let the Committee members decide what they want to do with this particular issue.

I think we need to go on to the next speaker. We've run over a little bit, but now we're going to run to parasite contamination, David Leiby.

In case you were interested, that little cartoon that I had running at the beginning of the talk was actually a Chagas organism in blood, so I fudged a little bit.

[Pause.]

DR. LEIBY: We're going to go ahead and move forward.

I've been asked to come here and talk to you about parasitic contamination. In fact, if one wants to think about the parasites that are possibly transfused by the blood supply, this is pretty much the short or long list, however you want to look at it.

There's a group of parasites that are highlighted here in white, and we aren't going to talk about those today because I'll deem those as being less important threats to the blood supply. The only one I'd qualify is perhaps Leishmaniasis. If you recall, about 10 years ago, we had some concerns about Leishmania after Operation Desert Storm. Seeing that we are now back in

the same part of the world, this may once again rear its head.

But I will talk today about these three or four organisms, and I'll briefly just call them by their disease names. I'll start with malaria, then move on to Chagas, talk a little bit about ehrlichiosis, in particular, human granulocytic ehrlichiosis, and then lastly I'll finish up with babesiosis.

First of all, I'll talk about malaria, and there's actually four agents listed here that are actually the etiologic agents of malaria, human malaria; those being Plasmodium falciparum, P. vivax, P. malariae, and P. Ovale, and vivax and falciparum are by far the ones of greatest concern.

As you can see, they're intracellular pathogens of red cells, so they have convenient vehicles for being transmitted by blood. They are mosquito-borne, generally by Anophelene mosquitoes, and primarily they're limited to the tropics throughout the world, and they cause what are generally characterized as flu-like symptoms, but then they have some periodicity, meaning that these symptoms reoccur every two, three or four days, depending upon the organism.

As I say here, it varies by the infecting species, and that has to do with the periods at which these parasites, and they are synchronized, and they

break out of the red cells. At that time, humans have reactions to the parasites in many of the products which they release.

Malaria certainly causes morbidity and mortality throughout the world and still is one of the number one killers of children.

What about transfusion transmission, particularly here in the United States? Well, our present prevention strategy relies solely on travel history. People are asked questions about where they've been, and if they've been to what is considered a malaria-endemic part of the world. They are deferred from blood donation for a certain period of time.

There are no screening tests available at this time. It's not something I think that's actively considered, but I'll maybe suggest that we should.

In the U.S., there are approximately one to two cases, transfusion-transmitted cases, of malaria per year. And generally these fall into two categories; the first one being an asymptomatic carrier, and that's going to be a common theme throughout all of these parasitic infections I'll talk about, is that the asymptomatic carriers are the ones we need to be most concerned about.

The others are semi-immune carriers or those in a semi-immune state; people who were infected long periods ago and appear to be, by all intents and

purposes, clear of the infection or partially immune, but can reacquire the infection or, in some cases, they have relapses of infections they've never lost, and some of these infections have been measured out 40 years after their initial appearance.

Now, when we talk about malaria and how it gets into the United States, generally, we think about international travel--individuals from here going international and coming back with malaria--or, in the case of people who have lived their lives in malaria-endemic countries coming here and living in the United States and bringing the infection with them.

As I mentioned before, our prevention strategy has largely depended upon travel history. However, in many cases, we are probably unnecessarily deferring blood donors because they got off the cruise ship in Cozumel or somewhere else for a brief shopping excursion, were never exposed to the parasite, were never there in the evening or the morning, when the parasite actually feeds, the mosquito actually feeds, I should say, and so we're actually deferring a lot of donors.

So, if anyone wants to consider a test for malaria, its greatest benefit may be, in fact, increasing the donor pool, as opposed to preventing transmission. As you see, as I said before, there's only been two transmissions.

The last one I'll talk about is something that we need to consider, what about endemic foci in the United States? These were a series of headlines that came out of the Washington Post just last year.

As you're aware, there is a malaria outbreak not too far from here, just up the Potomac, and what it turned out to be was that there were two teenage boys in Loudon County who were infected with malaria. That was Plasmodium vivax, I believe. They did not live near one another, at least they were far enough apart that the source was not the same, and as they went farther, they found that there was actually some infected mosquitoes on some of the islands in the Potomac.

As I understand it, the thinking is that there are some actually sod farms on the islands in the Potomac, in which there were some immigrants from parts of Latin America who work there, and perhaps they were the source of the malaria infection, but whatever it was, they got into the local mosquitoes. So down the road we need to consider whether or not malaria may once again become endemic in parts of the United States.

Let me shift gears to something a little different, something that probably poses a much greater concern to the blood supply, and that's Trypanosoma cruzi.

Here, you can see it's a very small protozoan parasite. This is actually the extracellular stage. You can see it's about the size of a red blood cell. It's not in a ring. It's just curled up there. It actually has a tail that goes there, you can see. Most importantly, it causes a chronic, asymptomatic, and perhaps most importantly, untreatable infection.

It's endemic to portions of Mexico, Central America and South America, and transmission primarily of our concern is by four routes, and I'll go over each one of these, briefly--vectoral, by an insect; congenital, from an infected mother to a child in her womb; via organ transplant; and, lastly, by blood transfusion.

Primarily, as I said, in a natural state, it's transmitted by the bug, and this is any one of a number of reduviid bugs that contains the parasite. Most interesting, unlike some of the mosquito-born agents that are transmitted by the front end of the bug, this one is transmitted by the back end of the bug.

So, actually, when the bug feeds and does take a blood meal, it defecates in the process and the parasites are in the feces of the bug. If that feces is rubbed into the bite wound or into other mucosal surfaces, like the eye of this young girl, the parasite can enter the human host. That's what is commonly called a chagoma.

It doesn't always occur, but it's a swelling at the site of the infection.

Here, again, we see the parasite in the blood, and eventually probably the most important area where the parasite ends up is in cardiac tissue. It causes cardiomyopathy and other complications in the heart, which will many times not be obvious for 20 or 30 years, but down the road can lead to serious complications and death.

Why is this parasite, if it's endemic to Latin America, of concern here? Well, quite simply, it's due to immigration, changing demographs. These are some statistics out of the 2000 Census that show there's about 12 million immigrants from Latin America. These are legal immigrants. Certainly, there are many more residents than that in this country, many who are also blood donors.

So we have a large population moving into the U.S. This is also 2000 Census data showing the great rise between 1990 and 2000 in the levels of Hispanic population. And if you read the headlines in the last couple days, I think, as of July, the Hispanic community is now the largest minority group in this country.

What about congenital transmission? We speak so much about the immigration population, but one thing I want to stress is we don't need to worry about that first

generation of immigrants of Chagas. We also need to be concerned about the second generation and the third generation because it does seem to pass down, in some cases, through the families.

And this is out of a study we did in Texas. We identified a donor in Waco, Texas, down here in the lower left, who was a 17-year-old boy who had Chagas disease or antibodies of Chagas. He was certainly infected.

What was interesting as we talked to this boy and his family, we found out that the older brother, who was also born in Texas, was also medicated for arrhythmias, and arrhythmias are one of the common characteristics of Chagas disease.

The mother, also born in Texas--see, all of these were born in Texas. Please take note of that. They weren't born in Latin America--was also medicated for arrhythmias, and her grandmother, who gave us most of this information, also was born in Texas a couple of generations back, with a history of heart ailments. She lost her brother, who died at 55 of an enlarged heart. Once again, another common characteristic of individual Chagas.

And what we think is happening here is this was all traced back to the great-grandmother, who actually immigrated from Monterrey, Mexico, who also died at a very early age of an enlarged heart.

Now, we tried to get these individuals in to test the whole family, to show that this is really an actual occurrence, and initially they agreed, and they became a little skittish in the end. I am not sure why. But we really suspect that this is probably passed down the maternal line, and there is literature out there that will support this contention. So this isn't just pie-in-the-sky.

Back last fall there was a great deal of concern about West Nile Virus, and I'm sure it hasn't gone away, and one of the things that really set this all off was the stories of West Nile being transmitted by organ donors. Well, before that, earlier in 2002, there was actually a report of a case of Chagas disease, which was transmitted by organ transplantation as well.

What happened was there was a single cadaver donor who actually the organs were split up among three recipients; one received a kidney and pancreas, another one received a liver, and actually the third one received the other kidney, and all three individuals, all three recipients came down with Chagas disease. In fact, one of them died of acute Chagasic myocarditis.

This is actually a blood smear from one of the recipients showing four trypanosomes in one field. That is quite unique to see that many parasites in a single field.

What was interesting anecdotal information I was told, when this donor recipient, when they pulled the organs, they also pulled the heart. When they looked at the heart, they found the heart to be riddled with I would say an extent of pathology that deemed it not worthy of being transplanted, and so it was just curious enough that obviously it was probably the damage from the parasite that made the heart not useful.

What about transfusion cases? There has been seven cases in the U.S. and Canada since 1987. These are seven cases that have been recognized, and that's an important point I'll talk about later. The most recent one, some you may not know about, occurred last year in Rhode Island.

One thing or two things I want you to notice in this that transfusion cases are not limited to people living in Texas border towns, Miami or in Los Angeles. Now, there are cases in California, Houston and Miami. You'll also notice one in New York City, two in Manitoba of all places, and one in Rhode Island. So they do appear in Northern climes, suggesting that there are individuals there who are infected and donate the blood, but you'll also notice that the donors were also immigrants from Latin America--Mexican, there's two from Bolivia, two from Paraguay, and lastly a Chilean donor.

So why so few transfusion cases, the question I get all of the time, and I think the answer is really rather simple. The reported cases that we see are, in fact, the sentinels or, if someone wants to say, the tip of the iceberg.

These individuals have all been immunosuppresed. They generate fulminant disease in which the parasites are very obvious. In some cases, they were detected in urine, other places very easily in blood smears. So these are the real obvious cases we see. More than likely, most of the cases are missed. These are the immunocompetent recipients, ones who may be diagnosed. Just to make this clear, most cases, in fact, are not even recognized.

A few years ago we did a study that was subsequently published in circulation, which we looked at over 11,000 cardiac surgery patients. We were actually looking at them from the standpoint of lookback because we were hoping to demonstrate transmission because cardiac surgery patients receive multiple blood transfusions.

What we found when we tested this repository that is held by Johns Hopkins, was that six out of the 11,000 or .05 percent were positive, they had Chagas disease. What was interesting was when we looked at the preoperative/postoperative samples, everyone had Chagas

prior to the operation, so no one got it through blood transfusion.

It was also interesting that when you do the numbers, and you look at the demographics of this 11,000 in this repository, 3 percent of the Hispanic population in this repository actually were positive for the parasite, had Chagas disease; in fact, these being cardiac surgery patients, some of them with cardiomyopathies and other arrhythmias and other associated problems that might be suggestive of Chagas disease.

Along with the fact that they were immigrants from Latin American countries, one might think the medical community would actually consider testing them for Chagas. Well, no, not a single one of these had any medical history of Chagas or any tests for Chagas disease. So it just points out that this is not something which physicians in this country, by and large, recognize, probably receive little training in medical school-- physicians here could back me up on that one-- and something that, unless it's very obvious as something, it's probably missed.

This is some of our seroprevalence data, studies we did in Los Angeles and Miami. It was published just last year, and it points out that in Los Angeles we looked at slightly over 1.1-million donations and a

smaller number in Miami. This is a study in which we asked a simple risk question: Were you born in Mexico, Central America or South America or have you spent more than six months?

As you can see, you can pretty significant populations will answer, yes, to your question. In L.A. it's 7 percent and in Miami it's 14 percent. Some have suggested just using that question of the deferred donors outright, and certainly with blood shortages, I don't think Miami would want to give up 14 percent of their donors.

If you follow these numbers down to the bottom, we tested them by EIA and then confirmed them by RIPA in my laboratory. The seropositivity rates were about 1 in 7,500 overall donors in L.A. and about 1 in 9,000 donors in Miami.

If one takes that L.A. data and begins to break it down, it becomes much more interesting. This is how it looks if you look at the data from 1968 through 1998. It's the years, and then this is the percent of donors who are positive or who have antibodies, but don't worry about this scale, just look at these numbers up here.

From 1996 through 1998, the rate of positive donors in L.A. incrementally increased from 1 in 9,900 to 1 in 7,200, to 1 in 5,400, and that is a significant increase. So what's going on? Well, we broke this data

down a little bit farther in another direction. We look at differences by donation type. This is the same data set broken down by allogeneic, apheresis and directed donors.

We found in the rates here that allogeneic was about 1 in 7,200; apheresis, 1 in 93,000; directed donors, 1 in 2,400. What we've found, as we looked through all of this and we started breaking it down and seeing who answered yes to the questions, we found a large number in the directed donors, 10.2 percent, and only 7.5 percent in the allogeneic. What it all really comes down to is the number of at-risk donors in your population who are donating.

So what was really happening during this time period, as we found out when we talked to the people in L.A., is because of changing donor demographics in L.A., they changed the recruitment efforts and started targeting Hispanic populations in Los Angeles. So as we began to change our demographics in this country, as I showed you the census data earlier, as the demographics change in this country, we are certainly going to be recruiting more Hispanic donors, and as we do that, we're likely to see increases in that number of positive individuals.

The other question I get, and we've done lookbacks at the Red Cross, is why haven't we

demonstrated transmission by lookback? Actually, we're 0 for 19. That's where you always keep striking out, some might say. Well, I'm going to tell you perhaps some reasons why we see that and maybe why this shouldn't be something that we hang onto and be of that great concern.

So what, we're 0 for 19, but we know transmission occurs in Latin America, somewhere on the order of between 13 and 49 percent of positive individuals are thought to transmit the infection. We see transfusion cases here in North America as well, so we know it actually happens.

In conjunction with the CDC, we actually looked at some of our seropositive donors. Some have said, well, they have antibodies. They're just not infected. Well, the general thinking is, once you're infected with this parasite, you are infected for life. In fact, when we tested our seropositive donors, we could demonstrate that 33 out of 52 were 63 percent were actually parasitemic. They had parasites circulating in their blood. So that means 63 percent of the time we were actually transfusing blood with parasites in it.

What is important, and I think is relevant, is that we found this parasitemia is intermittent. It wasn't there every time we tested, even on individual donors. We could test them one time, we could not

demonstrate parasitemia. The next time we would test them it was there.

What was also interesting and relevant to our lookbacks is, if you break down this 19 by the products, the recipients received, we found that 11 were red cells, 3 were FFP, 2 cryo and then 3 platelet units, and we kind of focused in on these platelet units because we thought, perhaps, platelet units are actually the one that causes the greatest amount of problem, as far as transmitting Ti cruzi.

In fact, if you look at excluding the last case in Rhode Island, at least five of the six reported transfusion cases in the United States have involved platelet units. Perhaps the reason why we see this is that platelet recipients tend to be more likely to be immunocompromised than those receiving red cell units, but our thinking also suggests that maybe Ti cruzi may separate with the platelets during whole-blood centrification. So we've actually done some survival studies in the lab, seeing how long the parasite survives, and where it ends up when it separates out.

What we've seen in whole blood, the parasite survives quite well up to about three weeks. In platelets, it seems to survive for at least four days. Considering the shelf life at present is five days, that means almost the entire shelf life of the platelet unit,

the parasites survive and are capable probably of transmitting infection.

Much to our surprise, the red cell units also do quite well, and the parasites again surviving up to three weeks. So there may be some discrepancy here, but it may then get back to who is immunocompromised or where we actually can detect the infection. Lastly, in plasma, we didn't see any parasite surviving.

So what about nationwide risk? Let me walk you through this slide. If we consider in this country there's 13.2 million donations per year, now, if each donor in this country donates, on average, 1.6 times, if we divide 13.2 by 1.6, we get 8.25 million donors per year in this country.

Now, based on some surveys we did nationally, we think probably about 2.5 percent of present donors are at risk. They have risk factors. They are born in endemic countries. So if we multiply 2.5 percent times 8.25 million donors, we have approximately 206,000 at-risk donors in the U.S.

Based on some of our studies in the laboratory and in other locations, we think about one out of every 625 of those will actually turn out to be seropositive donors. They will confirm as being infected. So that leaves us with 330 seropositive donors.

Once again, if each one of these donors donates 1.6 times, we likely have 528 seropositive donations per year in the U.S. Now, if each of those donations, on average, is broken down into 1.17 components, we have at least 618 potentially infectious components transfused or produced in this country each year, not necessarily transfused.

Keep in mind, this is all based on at-risk donors. That doesn't include congenitally acquired infections. So, in many ways, this can be considered as a conservative estimate.

Let me shift gears to the last phase which I'll talk about. I grouped these together because these are all organisms transmitted by ticks. If you look at the infections, this is the big three so to speak, that are all transmitted by the same tick, the deer tick, Ixodes scapularis. Those are Lyme disease, human granulocytic ehrlichiosis and babesiosis.

First of all, I'll qualify this by saying I'm not going to talk about Lyme disease. There has, to my knowledge, never been a transfusion case involving Lyme disease, much maybe to our surprise. There are certainly explanations that the spirochete does not survive well under blood bank conditions. The period of spirochetemia in the donors may be very short, but the bottom line is we have not seen a transfusion case, so I'm going to

focus on these two, in which there has been transfusion cases.

Now, this life cycle, by and large, involves a group of animals. There are deer involved, not because the deer are actually reservoir hosts, but they are actually good places where these ticks, the adult ticks live, and eventually lay their eggs and so forth. They're actually good transport hosts, too, because they travel quite far so they can take the ticks quite a distance.

The real culprit is this little guy, the white-footed mouse, who is actually the reservoir host for babesiosis and Lyme and so forth, perhaps bartonellosis. We'll come back maybe in a couple of years about that one, but we're finding new organisms all the time.

The first one I'm going to talk about is the agent of human granulocytic ehrlichiosis, now called anaplasma phagocytophilum. Its name changes quite frequently it seems these days. Not too long ago, it was always just known as the agent--I always found kind of funny--the agent of human granulocytic ehrlichiosis.

Then, for a while, everyone called it ehrlichios species, and then it was renamed ehrlichia phagocytophilum. Then, most recently in some paper by Steve Dumler's group in Hopkins, it was renamed anaplasma phagocytophila, with an "A" on the end. Actually, I

published a paper. It came out in the December issue of Transfusion that had anaplasma phagocytophila in the title, and then I saw another paper somewhere and it had the "u-m" on the end. So I sent an e-mail to Steve and said, "What the heck is going on here?"

And he said, "Well, the Bacteria Systematic people don't think it should have an "A" on the end because that's plural. So now the correct terminology, the latest is a "u-m" on the end.

The important thing is it's actually rickettsia. It's newly emergent and appeared in 1994. There are a series of agents that have just come out in the last 10 years that are of some concern. It actually lives, as the name suggests, inside granulocytes, and actually the parasite is this little circular thing living in what's called a morula.

It is, in fact, a tick-born zoonosis; again, the same tick, I. scapularis. On the West Coast, the thinking is maybe it's I. pacificus, Ixodes pacificus.

As with most of these agents, the symptoms are generally mild and flu-like. However, there can be severe symptoms--renal failure, gastrointestinal bleeding, secondary infection, and 5-percent fatality rate. If you can diagnose incorrectly, treatment is not too bad--Doxycycline.

What about the seroprevalence of this organism? Well, we did a couple of studies, one which we just published, and was using samples we collected in 1996 in Wisconsin and Connecticut. In Wisconsin we found about 5 out of 1,000 or .5 percent of donors had antibodies to this parasite. In Connecticut the levels were surprisingly 3.5 percent. It's not so surprising any more, because we've used samples collected in 2001, on which we found almost the same rate, again, 4.1 percent of donors have antibodies to this parasite.

Well, what about transfusion transmission? Well, there has been a case involving this parasite. It was actually reported in Minnesota, involving a red-cell unit. It was confirmed by symptoms, serology, 1:512 antibody titer as well as PCR. The donor involved had a history of lyme disease, extensive tick bites, and a very high serology, a very high antibody titer for this parasite. Certainly the history of lyme disease suggests exposure to the ticks, and we know that these ticks can carry two or three of these organisms. In fact, these ticks can transmit two or three of these at the same time.

The agent also survives quite well in blood, at least 18 days in laboratory experiments, and based on this transfusion case, we know it can survive at least 30 days in blood banks.

So given some of the seroprevalence figures I gave you, why don't we see more cases? Well, first of all, it's most likely misdiagnosed. Flu-like symptoms could be lots of things. Probably subclinical, and some of the thinking, and talking to some of my colleagues at the CDC, is that it likely has a very short bacteremic base, so donors who are infected have a very narrow window in which they can transmit the infection through blood transfusion.

And one last possibility is the fact that much of the blood in this country now is leukoreduced. Considering that the parasite is inside granulocytes, may be in fact pulling out most of the granulocytes that contain the parasite.

And last but not least is Babesia, certainly an up and coming agent, as you'll see. This is the agent of babesiosis, once again like malaria, and it's a very close cousin of malaria, actually in the same group, lives, resides within red blood cells. Again, carried by the same tick, as I showed you before, causes flu, malaria-like symptoms. Infections are generally asymptomatic or self limiting. Most of us can handle Babesia quite well. For those of who can't there are antibiotics that can be used to treat the infection. However, it can be severe and/or fatal, primarily in people who are elderly, immunocompromised and asplenic.

And I think that last three, elderly, immunocompromised and asplenic, all tend to be people who get a lot of blood donations.

When one looks at the geographical distribution of this parasite, the transmission or the distribution is actually expanding. B. microti is largely in two foci, one the upper midwest, Minnesota and Wisconsin, and one in the northeast, New York and New Jersey and Rhode Island and Connecticut as well as Massachusetts.

And within the last 10 years there's been this group of what are called Babesia-like organisms, and they're designated by the state they are found, but we commonly call them WA-1, MO-1, et cetera, for California and Washington and for Missouri.

What's interesting about these, there's been at least two transfusion cases of this new parasite, WA-1 already, and they're endemic ranges appear to be expanding. It's one of those instances I think, when we start looking for these organisms we find them. What's also appeared within the last year is the description of B. divergens, Babesia divergens, which actually is a cattle parasite which causes most of the Babesia, human babesiosis cases in Europe, and actually causes a much more severe disease. And it was found in Kentucky. There's some thought that this MO-1 parasite in Missouri may in fact be B. divergens, so this is certainly an area

or a consideration for these organisms that's rapidly growing.

Well, what about transfusion cases with Babesia? I up this figure all the time, and I think it's reasonable. It's probably even much greater than this, but I think there's at least 50 known cases of transfusion-transmitted babesiosis at this point from 1979. Most of the cases at this point aren't published because I think most individuals feel everything that's said about it has been said about it, and so these cases just aren't getting into literature. But those of who know, and the CDC, the Red Cross, up through New York and Connecticut health departments, we certainly are aware of these cases.

The recipients are anywhere from neonates to 79 years of age, and as I said, most of them are immunocompromised. Platelets and red cells have been involved. Of course platelets can be contaminated by red cells, so if red cells are infected they can be transmitted through platelets, up to 35 days, so basically almost for the entire shelf life of the red cell unit. About 2 to 8 weeks is the incubation period in the recipient.

And lastly, these infections can be identified by a variety of techniques, including serology, PCR and/or animal inoculations. What that refers to is

hamsters are actually exquisitely sensitive to infection of Babesia, so if you inoculate a hamster with human blood and then do a little smear on the blood at weekly intervals, you can actually pick up the infection.

How much is known about seroprevalence of Babesia in this country? And the answer is, well, not that much. There's been a series of studies that's shown the rates anywhere from .3 to as high as 9.5 percent from a variety of individuals. However, very few of these studies have actually been done on blood donors. There was an early study in Cape Cod by Marc Papovsky, showed about 3.7 percent of donors are positive. One in 2000 by Jean Linden, 4.3 percent. And then we published some recently in Wisconsin and Connecticut showing slightly lower numbers. The important thing though I think is that there is a fair amount of Babesia out there in the general population as well as in blood donors.

One of the questions that came to mind rather quickly was why not just defer donors based on tick bites? Well, we sent out some postcards to a variety of donors in quite distinct, geographically distinct areas, and asked them a simple question, if they had been bitten by a tick in the last six years. Surprisingly, out of 6,000 postcards, we got 2,400 back. What we found was that 4 percent of the donors actually reported a tick bite within the last year, and what was particularly

interesting was the difference in some of these regions, blood collection regions.

In Tulsa, Oklahoma, 9 percent of the donors reported they had been bitten by a tick in the last six months. Similarly in Atlanta, down near the CDC, 8.4 percent. Once again, deferring donors based on this criteria alone would certainly be unacceptable.

What we did notice was that donors were also very good at distinguishing large and small ticks. And from this standpoint we were trying to differentiate large ticks being dog ticks versus the smaller deer ticks. And the donors seemed to quite good at that as well. And as you can see, a large number of the smaller ticks.

One thing I should point out is that when you talk about tick-borne transmitted diseases, most individuals--and this is true of lyme disease, babesiosis--most infected individuals do not recall a tick bite, as I'll show you. In fact, when we looked at the seroprevalence of tick bits, we thought maybe the next level, if we can't defer them based on a tick bite, maybe we could test donors who report a tick bite. And this was published just a couple of months ago. And if we looked at individuals with tick bites and those who are controls from Connecticut, we found that the percent positive was virtually the same, .3 versus .4 percent.

So actually asking people about tick bites was of little use. In fact, as we talked to some of these donors in more detail, we think that maybe asking donors about a tick bite may be actually negatively select them, because those who report tick bites are the ones who are looking for the ticks. Those are the ones, who after they come in from outside, check themselves out. Those are the ones who probably use DEET when they go outside. So it's the ones who don't look for ticks that may be the ones we ought to be worried about.

We've done some studies in Connecticut too, and some of these are ongoing. This was an early study in 1999 comparing endemic and nonendemic regions. There again, these are arbitrary lines. Certainly there are ticks that are infected all through the central part of Connecticut. I mean they do cross that line. If you look at the endemic versus nonendemic areas, we had roughly--not roughly--we had the same number of donors, 1,745, and the percent infected was, in the endemic area, 1.4 percent; in nonendemic was .3 percent. Gave us an overall rate in Connecticut in 1999 of almost 1 percent of the blood donors.

Well, that was the antibodies. What about whether or not they had the parasite? We called back 19 of those seropositive donors from 1999 and we did PCR on them, nested PCR, and we found that 10 out of 19 or 53

percent of them had the parasite in their blood system. Once again, not unlike Chagas disease, a fairly large number of donors were in fact parasitemic, capable of transmitting infection.

That led us to an interesting study which is still ongoing, and it's actually a cooperative agreement the Red Cross has with the CDC to look at the issues of serology and parasitemia, how all these things relate with blood donors. And as I said, it's a 3-year study. It's actually kind of going into its fourth summer. And actually we're enrolling seropositive donors, donors who have antibodies to B. microti. And every 30, 60 days we're testing them by serology, blood smear, PCR, hamster inoculation, and also we're asking them a brief questionnaire to find out if they've been exposed to ticks in the interim, see if they've become reinfected or what maybe is going on. And as I said, we're looking for the relationship, if any, between serology and parasitemia.

This is the compilation of data from the three summers which we did this, once again about the same number each year, from about 2,100 up to about 2,600 donors. Seroprevalence rates, very, very little, from .8 this year, as high as 1.4 last year. Again, we think it's probably about 1 percent each year in Connecticut. When one looks at the PCR rates there was some

differences, as in '99 we had 53 percent, in 2000 it was 56 percent. Then it dropped to 8, and back up to 14 this year. The hamster rates are also variable, a little bit less, not quite as sensitive.

But what was interesting is the question why does the rate change so much from a couple years being in the 50s to lower rates? Well, if we look at these--first of all, all the donors smear negative, so we can't really detect them by blood smear, it's not sensitive enough. Several of the donors were actually repeatedly or intermittently PCR position and I'll show you some individual data.

And then lastly, the differences in PCR positivity. These infections of Babesia in general are certainly affected by climactic and ecologic factors. The ticks themselves have two-year life cycles. So what happens, one winter may have a very important effect on what happens to the ticks the following year and their ability to transmit infection. Certainly this being a very cold winter, ticks don't do well in cold winters unless it's very snowy, because then the snow protects them. So it will be interesting to see what happens after this winter being cold for a change. Climactic and ecologic factors effects the other hosts involved, the deer population as well as the rodent population. So all

these things are tied into why we might see differences year to year.

The other factor is, for old donors, we're actually deferring all IFA positive donors, so we may be in fact pulling out of the donor pool those donors who are actually most susceptible and most likely to be parasitemic. Perhaps we'll learn more about that.

A couple more slide, then I'll be done. And this one is just a few slides about some of our donors in the study. This is typical of what we've seen. This is subject 1426, first identified in July of 2000. We followed him every couple of months after that. Initially they had a titer of 1:512. When they came back, were entered in the study, they were at 1:256, and they were parasitemic both by PCR and hamster. Within the next couple of draws the parasitemic went away. As you can see, the antibody titer dropped below baseline, and they were released from the study. This is what we would typically expect to see, someone was infected, parasitemic, clears the infection and is fine.

Then we have donors like this, and this is not a uncommon occurrence, donor 2348, first identified in August 2000, very high IFA. Again, parasitemic. Was treated actually for babesiosis, received a 10-day treatment I believe of clindamycin and quinine. No longer parasitemic and has not been since then. But for

that time--and we're now I think somewhere into December of last year, so we're a good 24 months along--the antibody titer of this individual has not dropped. So we're not really sure what this means, but it's not out of the question that this individual can in fact be a chronic carrier, someone who was infected with Babesia and does not clear the infection.

And these are the kind of individuals that concern us as far as blood donation. What do you do if someone who still has an antibody titer, but yet you can't measure parasitemia?

Then the other category donors we see, starting now to see on some basis, is like this one, 1078. Once again a lower antibody titer, was both parasitemic by both methods, cleared the parasitemia. And as we got down to this level, by ELISA as well as IFA, was at baseline. In fact our criteria for removing these donors from our study was after three months of being negative on all tests, they are dropped from the study. So we thought when this donor came back in May, would have another low titer and be dropped. Well, suddenly the levels jumped back up and have remained that way since then, although they're right around the cutoff, which suggests this person may have been re-exposed to the agent. It's not surprising because most of these individuals live on large properties, which they have

deer on their properties and probably have a chance for re-exposure, even though we couldn't measure it be parasitemia.

Perhaps the most interesting data I'll show you is from our lookback investigations. These involved individuals in Red Cross who had previous donations from IFA positive and/or parasitemic donors, and we went back as far as 12 months. Recipients were then tested by IFA and PCR, and this is ongoing, but we've had 44 donors who donated or 118 donations. And if one looks at the data--and let's just go right to the bottom; this is the most important part--number of products transfused is 204. The number of recipients we've tested out of these is 28, and the number of recipients that are positive by antibody and PCR is 7. 25 percent of the recipients of the blood were infected by this parasite. So one out of four. That's, I would have to say, a pretty high transfusion rate, and certainly increases the concern for this organism.

So in summary then, I'll say that parasitic agents pose an ongoing and increasing risk to blood safety. Most importantly these infected donors are not often or almost always asymptomatic. They appear to be quite healthy. Even those ones who have infections with things like Babesia and Chagas disease, outwardly most times don't even know they're infected.

The implications for recipients certainly vary. As I said, in most cases recipients go unrecognized. In some cases, like Babesia, we can give them antibiotics, but in some cases like Chagas disease, it's an untreatable infection. Might as well forget it now about question strategies because they by and large lack sensitivity and specificity.

A problem now for all of these agents is that licensed tests are unavailable, so if we make the decision today--not we--if you would make the decision that we need to test the blood supply, at this point there are no licensed tests available for any of these agents. That also brings up always the question, what potential role might pathogen and activation have? If we could just implement, if we had effective methods of pathogen activation, perhaps all these agents could be eliminated as well, but then again that's the promise of pathogen activation.

So what about donor management strategies? I'll just give you four possibilities here. First one for malaria, we are already doing questioning, and it seems to do quite well for the most part with only one or two transfusion cases per year. But I raise the issues of screening, not from the standpoint so much as preventing infections, you know, perhaps it would prevent those

other two before increasing the number of donors in the donor pool.

Chagas disease seems to be that we are moving towards universal screening, and I think Jay can correct me if I'm wrong, but at the BPAC meeting in September the FDA expressed an interest in having manufacturers submit tests for blood screening for t. cruzi, and they suggested that if such a test was submitted and approved, that we would perhaps move towards screening the blood supply for Chagas.

HGE is just something that we need to monitor more. There's been very little information. However, perhaps leukoreduction is already doing the job, but some studies of that nature actually would be beneficial.

Now, babesiosis is perhaps a little more complicated, but there are some possible solutions. Certainly because we see this early parasitemic phase, this is the one we might consider NAT screening. I would not suggest NAT screening for Chagas disease because these are individuals who are infected as children and they have very strong antibody titers, so they are easily detected. And babesiosis certainly has window periods where NAT screening may be involved. Certainly blood screening situations are something for consideration. However, given its regional nature and the fact that most individuals can handle infection quite well, the route to

go here may in fact by the CMV model, in which we provide tested units for individuals who are at risk.

Now, since this is a panel that's trying to prioritize the issues, I thought for your help, your sake, I'd prioritize the parasites. This is my own list. So if I would prioritize these as standing, I would put Chagas and babesiosis as 1A and 1B. Always the problem here is while there's lots of cases of transfusion babesiosis, but which would you rather get, babesiosis or Chagas? I think it would opt for the treatable one. But either way, I think these are both ones that are worthy of consideration.

Certainly granulocytic ehrlichiosis is right up there as No. 3 and I would now put malaria as 4, but if we start establishing endemic populations of the parasite in this country, maybe that's something else we should consider, and certainly all the other agents.

Thanks you.

DR. BRECHER: Thank you, Dave. That was a very nice review, very comprehensive.

We have time for a couple questions and comments. Jean?

DR. LINDEN: Thank you very much. That was a truly excellent summary. I just have one very quick question on the Chagas. You mentioned finding I believe

that 63 percent of the donors are parasitemic, which I understood was at some point, not on a single test.

DR. LEIBY: Correct.

DR. LINDEN: So how many tests did you do and over what time period?

DR. LEIBY: The maximum number of tests we did was three, and so most of them were--we saw various patterns. Some people were positive on more than one test. Some it was every other test, and so it really varied. And what you have to keep in mind is that not only are they intermittently parasitemic, the levels in the blood bank may be low, and all the problems with PCR is that you're taking a small sample. So if the organism's not in the small sample you take, you may in fact be missing it. So it gets back to what Mark said, while we can't the whole unit, we're testing a small portion

DR. LINDEN: And those three tests were over what time period?

DR. LEIBY: Over anywhere from about 3 to 6 or 9 months, depending on the cooperation of the donor, which was sometimes quite difficult.

DR. BRECHER: Celso, want to ask if it's automated?

[Laughter.]

DR. BIANCO: Two issues, David, and I have to concur it was an excellent summary. In your last point with babesiosis and the lookback, I don't think that you were saying that those cases are transfusion transmitted. Your past experience with Chagas showed that a lot of those people with Chagas were positive. All these patients may be coming from endemic areas, may have been infected before.

DR. LEIBY: Well, I'll address that. If you look at the rate there as 25 percent, our transmission rate, and if the rate in Connecticut is only 1 percent, it's very unlikely that all those individuals would get it through--

DR. BIANCO: Well, I think we need more than that. The other point, and I think a point that you raised very appropriately about priorities and that is the them of this Committee, I think that we have to put those--and I want your opinion--all these agents under a bigger picture and context. Certainly you put the priorities for the parasites, but you didn't include them into the bigger issue of priorities. Do we do first bacterial contamination or Chagas, or bacterial detection or Chagas?

The second issue, I think that we have, and you have, particularly with all these years that you have dedicated to that, looked at the issue of transmission of

parasites by blood in the classical setting of donor prevalence and lookback. But I--and I want Dr. Chamberland--I'd like to see more the other side. That is, to have 7 cases of Chagas in 15 years, but you have 50 of babesiosis in 50 years or 30 years, that are being followed, one of HGE. All of them are less than what we have in malaria every year. And there is something that when you look at Chagas and you see 618 positive individuals and you don't hear about it, you have 7 cases in 15 years, there is something where the clinical implication of those transmission, even if they are occurring, does not appear to be significant so that was picked up by the clinicians. Yet, people are not informed by Chagas. People don't look for it. But in the higher contest of priorities I wish we could have a more national epidemiological look at the impact of those diseases in the country with the only one for which I know there is serious follow up is lyme disease. But so that we could see the other side of the picture, what is the prevalence in the population, what is the impact. And then go back and see how many of those were recipients of transfusion and how much of that transmission could be attributed to transfusion.

And I think that is very important experience, particularly in South America, where over the years with better protection methods for instance for Chagas,

transfusion became the most important means of transmitting Chagas in the '80s because people were so effective in combatting the vector and all the other things, and so transfusion became really the focus.

I'm open to your comments.

DR. LEIBY: I think that is the challenge the Committee faces, is actually prioritizing these agents, and I'm not going to try to pit bacteria against parasites or those kind of things. That's your job, not mine I guess.

I would say though that if you look at Chagas, obviously Babesia if there's a lot of transfusion cases, and there again, I'm sure there's many more than that we're not seeing. I think Jean will agree with that. In Babesia I would say there's probably 5 to 10 cases per year at this point that we know about. Chagas, I go back to the point that, yeah, there's only been 7 cases, but you know if the rate in Los Angeles was up to 1 in 5,400 donors, and if we know that 63 percent of those donors are parasitemic, then you have to ask the question: are you willing to transfuse that blood that has parasites in it? And then I think that becomes the bottom line.

DR. BIANCO: What we have to understand is the disconnect, David, and you as the expert--and we're talking about experts since yesterday here--has to help us understand the disconnect. That is if you have 63

percent of the people that are positive on PCR, those parasites are in the unit of blood. If you go to any more experiments, at least in mouse models of Chagas, you can transmit with one or two bugs.

DR. LEIBY: Sure.

DR. BIANCO: What's happened?

DR. LEIBY: I think they are being transmitted, and I think the cases are there. I think the people are just not being recognized. That was the whole point of the early slide, the cases that we do see are the obvious fulminant cases. And I think the other ones are there, and I think those donors, those recipients, 20, 30, 40 years down the road are going to have the cardiomyopathies and the other problems.

DR. BIANCO: Are there studies of frequent or particular patients like thalassemias and others in areas like LA or New York, to see the frequency or the prevalence of those markers in those individuals that are receiving red cells every couple weeks?

DR. LEIBY: And the answer is no, of course. You know that as well as I do. But I still it gets back to--I mean you're looking for concrete studies, and I'm not sure at this point, generating more studies for something we already know about. I mean you know the South American experience. You just cited it yourself quite correctly, that South Americans have made great

strides, and that in fact, yes, transfusion is the greatest or the primary way Chagas is transmitted in Latin America these days because they've, in many cases, eliminated vectorial transmission. And the same lines, all of Latin America tests for T. cruzi, even Mexico now, and we don't. And yet we see this recurring cases, and I think we cannot bury our heads in the sands because we can't demonstrate these by lookback when we know in fact it occurs.

DR. BRECHER: I think since we're running behind, we're going to have to stop now. Why don't we take a 10-minute break and we'll come back.

[Brief recess.]

DR. BRECHER: Everyone take their seats, please. We're now going to move on to pathogen reduction. Steve, are you ready? It's all yours, Steve.

DR. WAGNER: Good morning. I've been asked to talk a bit about pathogen reduction in cellular blood components, and I'll try to give an overview and a bit of perspective on this subject.

There's a number of rationale for pathogen reduction or inactivation. Everyone recognizes that there is some residual infectivity in blood, even in potentially tested products because of window periods and whatnot. There was a great concern, obviously, for plasma products that are pooled, and I'd like to remind

everyone that platelets are pooled as well, platelets derived from whole blood. And so that also is a rationale because that increases probability that an infected unit could be combined with others.

Pathogen inactivation might constitute an additional layer of safety beyond all the donor deferral mechanisms that we have in place now with respect to questions or infectious disease tests.

Pathogen inactivation has been suggested for agents that we are familiar with but for which we have no test, and I think David Leiby and Mark Brecher have gone over some of those agents this morning.

In addition, there are agents that we are well aware of which may mutate and might not be detected in a mutated form, and so it's been suggested that pathogen inactivation might be useful for these variant agents.

And, finally, there are those who believe that pathogen inactivation might be very effective against new agents, and I think this is somewhat controversial because one might--one would have to show that a particular method would be active against all agents to be sure--not even be sure, to hope that it might effective against new agents. But the argument has been put forth.

Then, finally, there's a great public and political expectation to have a zero risk blood supply, difficult though it might be.

There are a number of challenges, though, to solving a pathogen reduction problem. First of all is that pathogens, as you saw with David's lecture occur in all different cell compartments. They can be extracellular. They can be intracellular. They can be pro-viral forms and they can also be virus-associated, for example, where a virus is attached to a white cell membrane.

One of the other difficult things to deal with in pathogen reduction is that the different pathogens are all different and they have different susceptibilities to a particular agent. And one good example is hepatitis A, which is a non-enveloped picornavirus which has a very closely knit or packed virus capsid structure, so the proteins are so tightly packed that very few molecules are small enough to go through the pores of the virus. This makes the virus quite insensitive to most known disinfectants and agents that might be used for pathogen reduction.

Then, finally, there are some agents that can be present in very high quantities in blood, attain very high titers. And most of the methods for pathogen reduction probably are neither robust enough to be able

to detect in a test system, the many number of logs that might need to be reduced--an example might be parvovirus B19--or it may just be very difficult using any one method to be able to inactivate all the infectious particles that might be present to prevent transmission.

There's a number of approaches to inactivation. Today I'll talk about those that have been used for cellular blood components. I'll talk about psoralens and, for example, S-59. I'll talk a bit about riboflavin. And for red cells I'll talk about what's called a FRALE compound, and I'll explain that a bit later, which is termed S303. And then another molecule called INACTINE. I'm not going to talk about plasma today.

S-59 is a psoralen. It's a heterocyclic aromatic structure made of three rings that line in a plane. It readily intercalates into nucleic acids because of its planar structure and also because it's an amphiophile. It's got a portion of the molecule that can form a positive charge that can potentially interact with a negative charge on the phosphate backbone of nucleic acids.

As I said before, psoralens intercalate between the bases of double-stranded regions of DNA, and also there are double-stranded regions of RNA as well. And upon the absorption of ultraviolet A light, psoralens can

make mono- and di-adducts with pyrimidine bases in nucleic acid. And the presence of these adducts prevents the subsequent nucleic acid replication. And the logic here is if you have something that goes against nucleic acid and you're working on a way to inactivate pathogens in platelets, well, the only nucleic acids in platelets is in mitochondrial DNA, which is not thought to be necessary for storage or for transfusion. And so it's possible to distinguish the pathogens from the platelets by using this target.

The investigators who are looking into this method prepare apheresis platelets, and it's suspended in a platelet additive solution. S-59 is added to the platelets, and the mixture is then transferred into a UVA-permeable plastic container. They then shine that UVA-permeable plastic container with light of the appropriate wavelength in the UVA region, and when that is finished--and it takes just a couple minutes, for the light exposure, at least--they transfer the platelets to another container, which contains an absorbing resin which removes a large amount of the free S-59 that's in solution.

I should mention, though, that it would not be expected to remove any S-59 which is bound to the cells in any way. And so that would be transfused with the unit.

The platelets then that contain much lower levels of reduced S-59 that are free, that are not bound, are transferred to a storage container.

S-59 is quite robust in inactivating enveloped extracellular viruses and intracellular viruses. In fact, there are some non-enveloped viruses that it's effective against, and the companies involved in this have begun to show some effectiveness for inactivation of some parasites.

As far as I know, since it is a nucleic acid agent, it will probably not be effective against prions. It is effective against both gram positive and gram negative organisms. It's probably not effective against bacterial spores; however, one might argue that spores, given time to incubate in a blood unit, would probably germinate and with time would grow up. And so that would speak to the fact that you might want to do the inactivation process not immediately after the blood was collected, but a little later to be able to let any spores that might be present to germinate.

In addition, S-59 is probably not effective against endotoxins since that's, again, not nucleic acid-based. An endotoxin, as you know, is a great risk for sepsis in transfusion-associated sepsis. So you could actually kill the organisms with the inactivation mechanism, yet transfuse enough endotoxin to kill an

individual. And what that speaks to is that you probably can't wait one or two days to do your inactivation process to give the possibility for the bacteria to completely grow up, because then you could accumulate endotoxin. And so there has to be a timing of the process in order to allow spores to germinate first, but not allow endotoxin to accumulate.

Another pathogen reduction process that's being investigated by a different company is based on riboflavin. As you know, riboflavin is a vitamin. Again, the common theme is this aromatic tricyclic, a planar structure that intercalates into nucleic acids. It's got a sugar for a tail. And there is some literature, certainly not as much as the psoralens, that riboflavin binds to DNA by intercalation. And in the presence of light riboflavin induces guanine oxidation, single-strand breaks in the formation of covalent adducts between riboflavin and nucleic acid.

And, similarly to what I just spoke about, riboflavin seems to be able to kill extracellular enveloped viruses, and there's some evidence for killing of intracellular viruses. Again, the same viruses that might be difficult to inactivate by some of the psoralens would probably be difficult to inactivate with riboflavin, those viruses that have very tightly packed capsid structures.

Riboflavin is probably not effective against prions, and the same thing goes for bacteria. Some bacteria have been demonstrated to be inactivated by riboflavin, but, again, one might not expect it to be active against spores or against endotoxin.

In riboflavin right now--let me back up. Riboflavin is being used predominantly for inactivation in platelets, although some work has been done in red cells.

This is a compound that's being developed. The company terms is a FRALE compound. It has a structural similarity to quinacrine mustard for use in red cells for inactivation. Quinacrine mustard is an alkylating agent. It's got a nitrogen mustard moiety coupled to an acridine ring so it intercalates into nucleic acids by the bases of the acridine ring and then forms covalent cross-links with the nitrogen mustard.

Quinacrine mustard is a known closterogenic(?) agent, and so it obviously would be difficult to use that in a blood supply. And what the investigators did was put an ester linkage in the middle of the octyl chain, and we'll ese what that does.

So these FRALE compounds stand for frangible anchor linker effector compounds, and the anchor, an acridine moiety of FRALE compounds, is responsible for intercalation between the bases of double-stranded

regions of DNA and RNA, and the nitrogen mustard moiety, or the effector of the FRALEs, make an adduct with nucleic acid bases. And the di-adducts form a cross-link between the nucleic acid strands that prevent subsequent nucleic acid replication of the pathogens. And like platelets, red cells contain no nucleic acid, so there's a way to distinguish the pathogens from the red cells.

The ester moiety in the FRALEs is what's termed the frangible linker, and with time, it hydrolyzes forming a negatively charged acridine compound that should not further interact with nucleic acids because nucleic acids are negatively charged and like charges repel. And, in addition, the investigators have used a removal device to reduce the concentration of remaining compound even after the hydrolyzation.

S-303 has a spectrum which is similar to the other compounds I spoke about. It inactivates enveloped extracellular viruses and intracellular viruses, some non-enveloped viruses. Because its major target is nucleic acid, it shouldn't be effective against prions. It can inactivate a wide range of bacteria but, again, is not effective against spores and probably not effective against endotoxin.

Even though all these agents I speak about are fairly specific for nucleic acids, there are side reactions that occur, and for FRALE compounds, one of the

consequences of using the FRALE compound is that it can react with surface proteins on the red cell membrane, and this is demonstrated by this FRALE compound called PIC-1. And if you use an antibody against acridine which would pick up the molecule and do flow cytometry, you can see it's binding to the red cell membrane compared to a control which contains no FRALE compound. And this is quite striking, the difference.

However, in the presence of glutathione, as you can see here, for example, at the 2 millimolar level, that binding can be reduced quite a bit towards but not to baseline values. So this is a situation again where there might be some binding of the compound to the red cells that might be transfused.

So if exogenously added glutathione reacts with the FRALE compound, and that acts with an extracellular quencher, and then--and if FRALE compounds can permeate cells and inactivate intracellular viruses, can FRALE compounds permeate red cells and deplete their intracellular glutathione pool? And that's a concern because there are some drugs that people take that interact with red cells and make red cells susceptible to lysis when glutathione levels are low. These are oxidant drugs.

And there are some patients, for example, those who are glutathione-deficient patients or reduced

glutathione levels, who might be more susceptible to an agent that might react with glutathione.

INACTINE is a different type of molecule that's being studied for use in red cells. It's a molecule that has--that is different than the others. It doesn't have this tricyclic aromatic ring structure. It does have a three-ring structure which is joined by an alkyl group that has a repeating positive charge. And the tail, the cationic tail, confers DNA binding to nucleic acids, presumably through interaction with the phosphate backbone of nucleic acid. It's said to stabilize the molecule, and one of the things that distinguishes this molecule from the others that I talked about is that its molecular weight is smaller. And so it's able to--its range of organisms that it can inactivate is a little bit broader, although still agents like hepatitis A might be challenging for this agent.

INACTINEs refer to compounds that have aziridine moiety, which is this tricyclic ring here, followed by alkyl groups. And you see the amino groups are the positively charged groups that might interact with the phosphate backbone. This one is called PEN 102, and the investigators are using another one for clinical trials called PEN 110.

The molecule primarily acts at the N7 region of guanine and forms an alkylation. I should mention also

that at least we know that ethyleneimine is an agent that causes cancer in animals.

The N7 adduct can stop replication of the pathogen, but it also--DNA repair enzymes can recognize this adduct and remove the base, which can lead to strand breakage, and so there's another--there's more than one mechanism of damaging the nucleic acid.

As I mentioned, INACTINE blocks nucleic acid replication, and this is just evidence of this from the company that's developing it. This is just a DNA sequencing reaction here, and you can see that if you allow the reaction to go to completion, you get very long high-molecular-weight products. But in the presence of INACTINE, you get lower-molecular-weight products. And if you notice that the stops here at C residues, which on the template would correspond to guanine bases, indicating that the stop is at guanine.

The inactivation process for INACTINE involves a typically collected red cell unit to which INACTINE is added or delivered, and this is incubated for a period of time. I believe it's at room temperature. And then there's an extensive removal step which involves automated washing many times, and this is an issue to what to do with the wash. Does it go down the sink? How is that processed? I'm not sure. But in the end, you have a pathogen-inactivated RBC unit.

And susceptible pathogens, again, include extracellular enveloped viruses and intracellular viruses. The range of non-enveloped viruses is probably broader than a number of the other methods because of the small size of the molecule. But, again, I think that hepatitis A would be a challenge for this molecule. The company has done some work with some parasites, and it looks like there may be some inactivation of some parasites.

There's been a claim by those who work with it that the washing step removes prion protein, but I would remind you that prion proteins tend to be a bit sticky and people have found them associated with platelets and some white cells, and I'm not sure that all the studies have been done yet to show that those are removed with this process.

In terms of bacteria, there seems to be evidence that it inactivates bacteria, and, again, I'm not sure about spores. I'm not sure if those studies have been done to show whether or not spores are sensitive or not.

With respect to endotoxin, I don't know. Perhaps someone needs to measure endotoxin levels before and after the washing process to see what occurs in that case.

So there's a number of challenges for pathogen reduction. Processing may lead to unwanted reduction in

cellular yields. Some of these have been documented in clinical trials. Although the agents may be specific for nucleic acid, as I said before, side reactions may occur. Some of the most notable ones are reactions, covalent adduct formation to lipids. In the case of psoralens, there's a good body of literature, scientific literature on that.

There is some literature on covalent reaction to proteins. You saw some data I presented on one of the FRALE compounds, and even ethyleneimine can form covalent bonds with some peptides.

To a lesser extent, you see protein alkylations with riboflavin and psoralen, but if you look hard enough, there are some literature to suggest that these might occur as well.

In addition, the compounds that are photochemicals, which are psoralens and riboflavins, they can generate reactive oxygen species, and so instead of going to adduct route, they can interact and product single oxygen or hydroxyl radicals or super-oxide. And these are species that are small that can diffuse, and the diffusion of these molecules can go to other places in cells. Often membrane is a site of damage for these types of oxygen radicals. And that could be responsible for damage to membranes, whether it be platelet membranes or red cell membranes.

And so side reactions may be responsible for the loss of survival or function of the blood component, and these losses of survival or function are modest for some of these agents in clinical trials but, nevertheless, has been observed.

The side reactions may be responsible for unwanted, low-frequency adverse events, because if you have covalent reactions to proteins, that might act as a haptin to which an antibody response could be generated. And so of concern, but not yet observed, are potential immunological reactions, including anaphylaxis. The other concern I had mentioned before, that there might be an increased sensitivity of blood cells to other pharmaceuticals, for example, oxidative drugs, if intracellular glutathione is depleted, and also some patients, for example, glucose 6 phosphate dehydrogenase deficiency, people with that that already have low glutathione, that might be a concern.

With some agents, an unexpected accidental exposure of the staff who are making some of these alkylating agents and other things, to the manufacturing, transportation, or blood center staff, that could lead to an increased genotoxic risk. And so you have to kind of weigh what the current safety of the blood supply is with what you might expect if these things might be implemented.

These low-frequency risks, which have not yet been measured, cannot be estimated from the results of Phase I to III clinical trials, and even with the system that has been studied the most, which is probably the psoralen, the current experience with any one of the pathogen reduction systems probably hasn't involved more than 400 or so, maybe 500 patients, who have been transfused with roughly three, four thousand units. And so if these events are rarer than that, then more experience would be necessary to measure a low-frequency adverse event.

So my own view is that evaluation of these methods requires measurement of these events, these low-frequency adverse events. So without implementation and long-term study, it may be difficult to predict the risk to blood bank workers or to recipients by accidental exposure or by residual drug. And this accidental exposure is real. Sometimes blood bags break. That may happen in the centrifuge occasionally. Even though the manufacturers wish it weren't so, some blood bags just have defects--pinholes or bad seals.

Without implementation and surveillance, it may be difficult to assess the risk of allergic or hypersensitivity or anaphylactic reactions in susceptible recipients caused by alkylations to proteins or by drug metabolites. And then, finally--and this is the bottom

line, I think--without implementation and long-term surveillance, it might be impossible to determine if the risk of fatal outcomes from implementing an inactivation process is greater than the current risk of fatalities from infectious disease transmission. And certainly you don't want to do more harm than good.

So what's the risk of fatality from transfusion-transmitted infectious diseases? And you guys have heard about this the last two days, so I probably don't need to talk about it very much. For HIV, it's probably less than 1 in 2 million units. For bacteria in platelets--and I'm citing the CDC study here. I know Mark mentioned a number that was more frequent. But fatality in platelets is at least 1 in 450,000 units, according to the CDC BaCON study. And in red cells, it's much less, about 1 in 7.7 million units.

Certainly for bacteria, it's possible that this number is quite a bit lower because of unreported events that you might not look for. But the bottom line is, no matter how you look at it, these are very small numbers. And so I think it would be that a pathogen reduction system has to be quite safe to pose less a risk than the reported risk of fatalities from transfusion-associated bacterial sepsis. And so that's an important point. Should bacterial screening be put into play, I think it would have to be even safer. The bar would be raised.

So, in conclusion, all methods target nucleic acids. The methods can reduce the infectious titer of extracellular and intracellular enveloped viruses. Some non-enveloped viruses, bacterial spores, endotoxins, and prions will probably not be susceptible to inactivation. Implementation and surveillance may be required to assess low-frequency risks. These low-frequency risks and their assessment is essential for establishing that fatalities from pathogen reduction, from a process of pathogen reduction are less than the current fatalities from infectious disease transmission. And, again, these potential side reactions of these agents against molecules that are not nucleic acids, they may be important to understanding some recipient reactions as well as to explain any loss of cellular function recovery or survival.

Thanks.

DR. BRECHER: Thank you, Steve.

Questions? Comments?

[No response.]

DR. BRECHER: Amazing. Oh, John?

DR. PENNER: The genetic toxicity with the very small amount of mustard-like agents, it's a little difficult for me to think that this is much of an event that can occur with the quantities we're talking about compared to what we use in our chemotherapeutic

approaches and the rather low incidence of mutations or carcinogenesis. Is that in your perspective?

DR. WAGNER: Well, it's kind of hard to measure in cancer patients who might reoccur whether their treatment with chemotherapeutic agents increases the risk of cancer. Some people believe so, but other people believe that reoccurrence occurs and metastasis in different cancers coming up. So I think it's a controversial question.

DR. PENNER: In addition, the pharmacists who handle most of our chemotherapeutic agents are certainly under the gun in exposure, and incidence has really not been revealed in this group, who, of course, take rather careful management of these products.

DR. WAGNER: Yes, I think that implementation of these sorts of agents might require that level of expertise and care to make sure that people aren't harmed. You have to have people that are knowledgeable and trained in order to reduce risk.

DR. GILCHER: You didn't remark about the possible advantage in emerging agents and potentially killing an emerging agent, and then potentially eliminating the need for additional testing. A good example would be West Nile.

DR. WAGNER: I didn't mention emerging agents. I didn't mention that that would enable you to not

implement a new test. I think that's possible. And I think what's evolving is that we're devising this testing strategy for blood that right now is involving adding one test after another to blood. But it doesn't seem alternatively that it's not an impossibility that in the future there may be tests that can deal with a whole number of agents on things like chips and other things that we can only imagine.

And so you have these two competing processes that are trying to get at the same question, and right now screening is in place, which determines a risk factor of the blood supply. And so that's the hurdle that the inactivation--the people who are trying to work with inactivation have to jump over to show that the safety of introducing the process is safer than the current risk.

DR. GOMPERTS: Thank you, Dr. Wagner, for your presentation, and focus on safety is obviously appropriate. But I do want to perhaps give you a little bit of perspective around pooled plasma products. In that situation, fortunately, we're in a pretty good situation today because there is both screening and viral inactivation, and it's the combination of those that certainly has brought us to that situation at this time.

The other point that would be useful--and I mentioned this to Dr. AuBuchon yesterday. It would be useful to get an overall risk of HIV plus HBV plus HCV

plus bacteria, et cetera, et cetera. You know, what is the overall risk from pathogen challenge and what would pathogen inactivation actually do?

DR. WAGNER: Okay. Let me take your first comment first. I agree that agents--well, let me take the second one. The last literature report of risks, aggregate risks in the literature was by Scribner, I believe, and it was roughly 1 in 38,000 or so units. I might be wrong, but it's close to that. But since that time, NAT testing has gone into place. HBV is probably down quite a bit, and really that particular number is totally driven by the most frequent event that occurs. And if you leave that to fatalities rather than just mere infection, you're probably looking at the bacterial number, which is somewhere between what Mark said it was, potentially, and what the CDC says it is. And that might be expected to be somewhere between 1 in 60,000 to 1 in 450,000 units of platelets.

What was your first comment, again? I don't want to leave that...

DR. GOMPERTS: The ideal situation, if one is targeting for an ideal circumstance, would be both screening as well as--

DR. WAGNER: Oh, yes, for the plasma. Yes, but plasma is a little bit of a different situation in that for at least the derivatives, they were being pooled in

immense size pools and distributed to many, many people for each pool. So screening is clearly not enough, and clearly there were well-documented transmissions.

Here we're talking about, for the most part, single components collected from an individual given at most to two or three people. You know, if you give plasma to one person, platelet to another, and red cell to another.

So I think the differences between plasma derivatives and cellular components are kind of orders of magnitude in terms of a risk situation. And since the recognition of the dangers of pooling, in addition we've reduced the pool sizes for plasma as well as institute testing and pathogen reduction techniques. And I think all of the strategies have worked well.

DR. BRECHER: Keith, the last question.

DR. HOOTS: In terms of the hydroxyl super-oxide electron (?) business with a couple of these, is there any evidence that if you just collect, treat, and then observe for the full life span of a red cell that the rate of hemolysis, natural decay of hemoglobin is in any way altered afterwards?

DR. WAGNER: Well, I think the only one that's been studied in red cells that I went over today is riboflavin. And I think the only published information

is one poster that Mike McAteer was the first author on. And I believe there was evidence of increased hemolysis.

DR. BRECHER: Although with some of the other molecules, at least in platelets, there's platelet damage from these molecules.

All right. Thank you, Steve--oh, Mike, one last question.

COLONEL FITZPATRICK: Yesterday we talked about the limitations of inactivation methods because of the load of the agent, and you didn't mention that. I just wondered if you could make a comment on where you see that.

DR. WAGNER: I did mention it in the very beginning. I think there's some agents that may be very high-titer viremias. Things that would be included in that might be parvovirus B19. It's not clear what the titer is in blood because people typically measure by PCR and there may not be a one-to-one correspondence between what you measure by PCR and what you might be able to see in an assay system. Also, the assay system for B19 is not as well developed as some of the other viruses.

If you look back and say, well, what about HIV, you know, what would happen if pathogen reduction were here--were implemented before any testing or knowledge of HIV took place, I think it would be difficult to make a determination with certainty that the units would be safe

to transfuse without transmission, because there's been measured as much as 10^8 PCR positive molecules per mL in blood at the peak of viremia in an asymptomatic individual. And you multiply that by 500 mLs of the blood unit, and you get up to five times 10^{10}. And notwithstanding that there are some defective particles, merely showing a 6-log inactivation may not guarantee that you're going to deal with all the infectious agents.

And so there's still going to be some uncertainty from a clinical standpoint if these methods are implemented whether or not infectious diseases would indeed be prevented from transmission.

DR. BRECHER: I think we need to move on. Thank you, Steve.

We're now going to have an update on prions by Bob Rowher.

DR. ROWHER: It will take me a second to swap computers here.

[Pause.]

DR. ROWHER: It's a pleasure to be here. Mac asked me to just give an update on the current status of the BSE, variant CJD problem, so I'm going to spend the first part of this talk talking about not specifically blood-based issues but issues surrounding the epidemiology of the diseases, and then in the second half of the talk, I'll focus more on blood-related issues

directly, including some new data, which most of you probably haven't seen, from our laboratory.

It's a little bit embarrassing to follow the previous speakers because we're talking about a disease for which there is no known instance in which a transmission has ever occurred that can be related to blood transfusion or the use of blood-derived products. And, rather, what's driving the interest in this and the concern is a precautionary interest, and that is that we're dealing with a disease that we don't understand very well. With the AIDS epidemic in the background, the concern is: Could something be happening with this disease that we're not detecting yet that will come to light in the future? And do we need to prepare ourselves for that now? And that's what we've been trying to do by the only tools that we really have at hand at the moment, and that's deferral.

This is a somewhat out-of-date slide, because it ends here about 2001, of the BSE, variant CJD epidemic. Just to remind you that we had--in light blue here, we had this epidemic. These are animals, cattle that were diagnosed with the disease, confirmed diagnosis indicated in this line here. This is the birth dates of these cattle back here and red is plotted on a very different scale; 1 to 10 here are the cases of variant CJD as they have come to light. Those cases add up to 133 cases as

of last September, which is the last time I updated--checked in on this.

And the concern is what is going on here with this variant CJD occurrence. Is this the beginning of something that's going to eventually look like this? Or are we looking at the peak of something that's already happening? We'll get into that a bit more in a minute.Now, there has been some data that's come to light just within the last year that addresses the prevalence of variant CJD carriers in the United Kingdom population. This was a study in which, unlike classical forms of CJD, variant CJD patients have evidence of the prion amyloid in their tonsils and appendix and some of the other lymphatics. So they can be distinguished on that basis as well as the fact that these--the amyloid from this disease gives a very distinctive pattern on a Western blot compared to classical forms of CJD.

A study was carried out. It took, unfortunately, about five or six years just to go through the ethics and all the issues of whether to notify, not notify, whether--do you identify the patients or not, et cetera. Eventually it got underway, and the net result was that of 8,318 specimens that were usable as specimens, they found a positive.

It's very hard to get a good statistic off one event. Nevertheless, statisticians will do their best,

and just taken at face value, this would be a prevalence rate of 120 per million, with a 95-percent confidence, somewhere between half to 900 per million. That works out in a 60 million population of somewhere between 30,000 and 54,000 cases incubating.

And, of course, the thing to remember about this is we have no idea what the ascertainment rate was in this type of study, but it's certainly less than 100 percent, and probably a lot less.

Hopefully, they will be able to put together a follow-up study involving another 10,000 samples so that maybe we can define this statistic a little better. But as far I know, that is not yet underway.

Oops. Let's see if I can--

[Laughter.]

DR. ROWHER: This has happened before. I'll switch to the arrows; then the danger is less.

The exposure to BSE was vast, and the estimate keeps going up. Within the last year it's now estimated that there were several million cattle actually that entered the food chain with BSE as opposed to a million that was estimated earlier. The meat and bone meal that came from these cattle was widely distributed throughout the world. The WHO has done a very nice study of that and for some reason, for political reasons, they're not

publishing that data. But they have these beautiful maps showing that it's really everywhere.

BSE is identified in virtually every--actual cases of BSE have been identified in every country in Europe. Japan has had cases. Surveillance is probably pretty good in Japan. We don't know what it's like in the rest of Asia and many other parts of the world. But it makes you wonder if it isn't more prevalent than we're currently aware of.

We have chronic wasting disease of deer in this country, and we have exported that to Korea during the last few years.

Variant CJD, the total cases are 133 cases of September of last year, with cases occurring in the U.K., Ireland, France, Italy, Canada, and the United States. The Canadian and United States cases undoubtedly originated in the U.K, but, nevertheless, they occurred here. That's why our deferral program is in place. Both of these people would have been deferred, which is somewhat reassuring in that regard.

The epidemiology, again, the incidence of these variant CJD cases has been very up and down. Statisticians say they see a trend, an upward trend. This is, again, only partial data at this point, variant CJD in red. And all I'm doing here is I've just shifted the variant CJD epidemic ten years back to the beginning

of the BSE epidemic and exploded the scale of--when BSE was occurring at this same rate, it was also showing a lot of fluctuation. And, of course, we know now that BSE cases were occurring all the way back in the early '80s. So it's not necessarily reassuring to see this, and, again, the big question is: Is this mapping to an event like this early in the BSE epidemic, or are we looking at cases that have been derived from the peak of the BSE epidemic? Which, of course, would be the most desirable case. However, that would make the incubation time quite short, and personally I doubt it.

Just a minute. That slide is out of place. That's what I'm going to talk about in terms of blood. But, meanwhile, I want to talk about some other things that have come out in the last year or two.

The oral route used to be considered, in the days when I was at NIH in the Guijesec (ph) lab, a very, very inefficient and unlikely route of transmission of these diseases. Attempts to transmit kuru across the species barrier, even into monkeys, never worked by the oral route. There were lots of attempts to transmit by the oral route into rodents. They didn't work either. And then we had BSE, which sort of changed our whole image of oral exposure.

BSE is definitely transmitted orally, and it's transmitted across the species barriers--to humans, cats,

antelopes, and sheep. Sheep are presumed to pass sheep scrapie orally, though that is a presumption and it's never been actually proven. But it's presumed how it's horizontally transmitted in the field.

Humans are presumed to acquire variant CJD orally, and CWD, the new kid on the block, has a very high virulence. It's horizontally transmitted, at least in white-tailed deer, and it's also presumed to be orally transmitted; i.e., we're getting a different picture of the oral transmission.

This paper, which just came out in 2003, by Bessen and his group is fascinating. He's showing that if you actually inject the tongue of a hamster with, in this case, transmissible mink encephalopathy, another TSE disease of mink, you get a very fast, direct infection of the brain. You can detect the PrP amyloid in the tongue within a couple weeks of inoculation. And you don't have to directly inject. If you just abrade the tongue and rub the stuff on, you get a similar type of transmission.

A warning sign that we've been thinking in terms of a gastric route of infection via the oral route, it may not be that. It may actually be coming through the tongue and the hypoglossal pathway.

Another alarming paper during the last year came out of Prusiner's lab, "Prions in Skeletal Muscle." I have read this paper again and again, and we are trying

to repeat this work now because it needs to be repeated--replicated. But basically they found in--these are not transgenic mice. There's nothing special about them. It's CD1 and FVB mice. They found that after an IC inoculation, they're recovering infectivity based on incubation time--not the best kind of measurement you could make, but based on incubation time that looks like it's about 10^5 to 10^6 infectious doses per gram of striated muscle taken from proximal hind legs, whatever that means.

If this is true and if this is generalizable, it means that the exposure to BSE was vastly greater than we had anticipated. The whole program of control in the United Kingdom was to throw away the presumed organs at risk, the specified bovine offals, and presuming that meat was safe. If meat, in fact, was not safe, the human exposure was huge.

Finally, I have to say a few things about CWD. CWD was really confined to the academic laboratories at the University of Colorado in Laramie for almost--well, it was first known in '67--'77, '87--20 years before we saw our first feral cases of this disease. These cases showed up just outside those compounds. As of today, we have it in--it's really all over the United States. It's being spread by commerce in these animals as well as it has moved into the white-tailed deer population. It

seems to be amazingly virulent in that animal, and I take as evidence of that the fact that in hunter kill surveys in the foci of incidence between Laramie and Fort Collins, from which this disease seems to be radiating in the wild, the incidence rate is 12 percent or higher. That's higher than you would ever see in an endogenously infected scrapie flock in Europe for sheep scrapie. So it's quite amazing.

There was an outbreak in Colorado, which we're--not Colorado, excuse me, Wisconsin among wild white-tailed deer. We're not sure of the origin of that, but it looks like probably animals were transported in there and spread the disease.

The incidence rate--the prevalence rate among those animals in an extensive cull of three counties was also very high. It was greater than 10 percent in the focal area. It's amazing.

This is a disease unlike--there's only one other TSE disease that we know that's horizontally spread, and that's sheep scrapie. This disease, in white-tailed deer especially, is horizontally spread for sure. It's in wild animals. It will be much harder to control than sheep were, and we've never been able to actually control the infection in sheep. It's now been exported to Korea, at least, and let's hope that it didn't get exported to

New Zealand, which has a very big industry in deer, including North American wapiti.

There have been some culls that have taken place of wild animals. It's very unlikely that these will be effective. It's almost impossible to get all the deer. And it's very likely that since these culls have been affected by hunters--hunters are recruited to do the culls--that a lot of the healthy-looking animals are being eaten, and that means that we're getting a lot of North American exposure to this disease as well.

Commerce is spreading the disease. Elk ranching is--we have 27 elk ranches in Pennsylvania just north of us here, or at least 27 permits for elk ranches have been issued in that state. They're being raised not for meat but for antlers, but when the animals get--when they do get an infected herd, they cull it and they're marketing the meat, which means we're getting more human exposure by that route.

Regulation is a nightmare. Wild animals are--the meat is actually controlled by the FDA, but the actual management of the animals is under hundreds of divisions of natural resource jurisdictions. The economic interests are being served first, the public health interests second, in my opinion at least, and we're making a lot of the same mistakes that we made with BSE. People are being encouraged to go ahead and eat the

meat. There's no known risk to humans so it must be okay. And there's no scientific basis for any of these risk assertions because we know very little about this disease.

The science is finally being funded. There's a major program at the University of Colorado now. Glenn Telling (ph) has a laboratory that's trying to create transgenic models so we can actually work with this thing in the laboratory. But much of the research is oriented towards the industry, the hunting industry and the deer management industry, as opposed to having a public health orientation.

CWD does need to be studied intensively because it is an outlier in the TSE field. It doesn't present as a neurological disease. It probably has a very different tissue distribution from other members of this class, and the infectivity probably has a different tissue distribution. And I think we can expect surprises.

I think it's curious that--I was looking through my notes trying to find when this meeting was, but one of the last meetings I attended of this committee, which was several years ago, there was a very big discussion of this that was not on the program but people got started on it, and Dr. Kaplan came to the conclusion that, yes, maybe we should be considering food as a potential risk to the blood supply, as a source of infections which

ultimately end up affecting the blood supply. And, in fact, this has turned out to be true, I think, in a way. We don't know that CWD is transmissible to humans and let's hope that it's not. But it's certainly something that I think this committee should be tracking.

I'm now going to move to a discussion of blood-borne TSE infectivity and what we've learned in the last few years about it. And I won't be able to go into this in any depth, but I'll give you the highlights here, and we'll touch on these issues.

First of all, we've done--most of the titrations of blood have been done in our laboratory in the hamster model, and we consistently get a range of values when titrating individual bloods that range between about 6 and 20 infectious doses per mL, and pools, where we pool the bloods from 20 or more animals, typically have a range between about 8 and 12 infectious doses per mL. So we use 10 as the typical average number in the laboratory when we're thinking about this.

We've now extended our studies to the 301 V mouse adapted BSE, variant CJD model which we have in the laboratory and have licensed from the Institute for Animal Health in Edinburgh. And in that model, we're getting, again, 10 to 20 infectious doses per mL.

There was an interesting--in the hamster model, we work with males. In the case of this particular

model, we're raising the animals--they're being custom-raised for us, and so we're using both sexes. And there was a difference. I'd like to see this again before I make anything out of it, but it was curious. The females seemed to have a higher titer than the males. It may have something to do with where they are in clinical disease when we sacrifice them for the assay, for the blood.

It's important to realize that even though this is a very low concentration of infectivity, it actually adds up to quite a bit on a per unit basis. And so 8 to 22 ID per mL comes out to 4,000 to 11,000 ID per 500 mL unit. And even though the IV route of infection is only about one-tenth--this is assayed by the intracellular route. The IV route is about one-tenth as efficient. That still leaves a lot of infectivity in a unit, 400 to about 1,000 ID per 500 mLs assayed. And it certainly should be enough for a transfusion transmission.

In fact, this has been borne out in sheep. Nora Hunter and Fiona Huston over the last few years have explored this possibility in sheep, transfusing 250 to 500 mLs per transfusion. They now have, if you take these papers together, two transfusion transmissions from sheep that have been experimentally infected with BSE. But they also have four transfusions from sheep that acquired sheep scrapie naturally. And this has been a

missing link in the blood-borne infectivity story because we had no known example of a naturally infected animal with blood-borne infectivity, and it had always been a nagging concern of mine that this was an artifact of the experimental route of transmission. I'll show you some data looking at that directly in the experimental models that suggests that that's probably not true and is supportive of this.

They also saw transfusions from preclinical as well as clinical animals, and this is entirely consistent with the hamster results which we developed prior to this. In the hamster model, we have a lot less blood to transfuse. We get about 4 mLs out a hamster. We take 2 mLs of that and do a 2-mL blood replacement in a recipient. This is what constitutes our hamster transfusions.

We have done about 100 hamster transfusions. It took several years to do them because they're a bit tedious to do, and staging it and that kind of thing was a problem. But what that adds up to is about 200 mLs of hamster blood transfused together if we had been able to transfuse it all at once. And out of that, we had three transmissions. This is less than we would have expected. We expected--on the basis of our titrations, we know that these bloods had somewhere between 60 and 300 infectious

doses by the IV route. And we would have expected to have infected most of these animals as a consequence.

So there is something--very definitely there is something different about the transfusion route, but if you transfuse enough blood there's enough infectivity there to cause a transfusion.

The sheep transfusions answer a question we had. In the case of the sheep transfusion, they're transfusing about 4 to 6 percent of the blood volume of the animal with 250 to 500 mLs. We're transfusing 33 percent of the blood volume of the animal, and it's not what proportion of the blood volume you transfuse. It's really the total volume that gets transfused that determines the infection efficiency.

Transfusion transmission to humans, there's no evidence for it, as I opened with that remark. The question is why. We don't know, but what we can say is that there is--blood infectivity now has been demonstrated in mice, hamsters, guinea pigs, sheep, the natural infection in sheep, and there's a report--I'm not sure of its credibility--of demonstration in lemurs. Blood infectivity has been found in the scrapie models, CJD models, variant CJD models, and GSS.

When you put this all together, I think it's very unlikely, even though we haven't had a

demonstration, that there is not infectivity in humans infected with the TSE agents.

On the other hand, as I'll show you in a minute, it's not because the infectivity gets removed with the buffy coat or by leukoreduction because only a portion of the infectivity is in the white blood cells.

This is a component separation, again, of hamster blood. This was a--I can't remember if it's 50 or 100 mLs of hamster blood. Oh, actually, it was 250 mLs of hamster blood is what we started with because we went on to cone fractionate this. But basically on the basis of volume, we get this type of separation. On the basis of infectivity--these bars are proportional to what was recovered. So on the basis of infectivity, 35 percent of the infectivity ended up in the buffy coat and 25 percent in the plasma and the red blood cells. We are missing 15 percent here. If you normalize back to 1, you'd get a distribution like this, 25, 45, 30. So you can take your pick what you want to consider here. But basically we've got about half of the infectivity in the buffy coat and the rest of it in plasma and red blood cells. We don't believe red blood cells themselves are intrinsically infected, but we have not proved that point. But we've finally worked out a way that we feel we can do it in a convincing way. We can actually make

the measurement in a convincing way, and we have that underway.

The buffy coat, of course, is this mish-mash of components, and some of that infectivity must be due to the plasma contamination. And that's probably where a lot of the red blood cell infectivity comes as well.

Well, we thought it might come from platelets because they contaminate all the components, and the fragments would survive in plasma. Even after fairly hard spin, we can see some. And platelets, at least in humans, contain significant quantities of PrPc. That's not true in hamsters and it's not a very strong effect in mice either.

When we actually looked at platelets purified by ficol from 22 mLs of blood containing 220 infectious doses, there was only one infection in the platelet fraction. And calculating--there was a volume loss there that would work out to about 3.5 here. And so we feel confident that the platelets is not--that's not where it's at. That's not what's carrying the infectivity.

This experiment was also interesting because in the mononuclear cell fraction, which we could not quantitate the recoveries of very well because of the way in which we purified the platelets; nevertheless, we would have expected way more than 22 infectious doses there. And so this and other circumstantial evidence

from our laboratory has us wondering if the infectivity is--just how tenaciously it is attached to white blood cells.

Now, we have since made another measurement of this by leukofiltration. Leukofiltration has been employed in the United Kingdom and Canada. It's been discussed in the United States not as a way to protect ourselves from variant CJD, but it's a hidden subtext wherever it's proposed as a means of reducing exposure to these agents because it is presumed that they will be cell-associated and in the white blood cell fraction.

Several attempts have been made to look at this using spiked samples. Leukofiltration didn't remove any of these spikes. We finally decided that the only way to do this, because it's kind of a finicky method, was to attempt to do a full-scale leukoreduction with a blood bag using titrable blood, which would be hamster blood. And we have managed to do this. We used endogenously infected blood from hamsters. We were able to collect 500 mLs from 150 hamsters in a couple hours in the morning with everybody in the lab working together, put it all in a blood bag and did a full-scale leukoreduction with that blood--a couple of them, actually. And we have done one limiting dilution titration using the--I think I've got it here, this Pall filter set, collection set.

And what we've actually measured here is the infectivity that we started with and compared it to the infectivity that's in the leukoreduced sample. And what I can tell you here, this will be presented in full at the CHI blood safety meeting in a month by Luisa Gregori in my lab who did much of the work here; that the filters performed according to specs. We removed 99 percent of the white blood cells, and we're only removing about 35 percent of the infectivity. So it's consistent with the component separation of the white blood cell fraction.

We also have done this separation, and we have all these components in the freezer, but we have not found the support to actually put these on and titrate them. So we've looked at--we have an RBC prep, a platelet concentrate, and PPP that could also be looked at.

One of the things that has bothered me, I have been concerned since we began this work that maybe what we were looking at was just a rodent-specific phenomenon. The sheep results have relieved that concern to a large extent, but, nevertheless, what I was concerned about is the spleen, and the spleen--when you stress a rodent, you can get an extravasation of the blood out of the spleen and the white blood cells. So I was thinking, well, when we put these animals up and anesthetize them for collecting--for exsanguination or something like that, is

something like this happening? Are we really just looking at infectivity that's sequestered in the spleen and gets released under these cases? Or is this stuff that circulates all the time in the blood? Do we have a true viremic condition?

And the reason you'd be concerned about this is that, next to the brain, the spleen has the highest concentrations of infectivity in the body. And so we decided to do a bunch of splenectomy experiments, and these were done by Joe Lazar in the lab. We did splenectomized--compared splenectomized animals with sham surgeries, and we have also been concerned that maybe the route of infection would be important in terms of the amount of infectivity in the blood. So we tried the oral route as well as the IC route that we usually use and IP route.

We adjusted the doses for similar incubation times for each route. We pooled the blood from 20 animals in each group, and then we assayed them. And the take-home here is that there was really no difference in the incubation times of the disease between animals that had been splenectomized or sham operated on that were infected by the oral route. The IP route had a shorter incubation time, but there was no difference between these two groups, nor here. So, really, the loss of the

spleen really had no effect on the course of the disease in the animals.

DR. ROWHER: And because this was an unsupported experiment, we used buffy coat inoculations to get an idea of the relative titers, and amazingly, there was no difference in the amount of infectivity in the blood, no statistically significant difference. If anything, there was more infectivity in the blood of the splenectomized animals versus the sham(?) surgery animals.

So in summary, there was no obvious effect. All three routes of inoculation resulted in infected blood, so the root of infection is not an important parameter here. The oral inoculation may produce lower titers, but I have a feeling that's an artifact of when we collected the animals. And if anything, the blood titers were greater in the splenectomized animals.

Another thing we've looked at is when the infectivity first appears in blood. This is an important public health question in terms of doing your risk evaluations because you have a CJD. We know CJD can incubate for 30 or 40 years in extreme cases. And so is that person pre-anemic during that entire period, or is it only a few weeks before we recognize them as having clinical disease? And we had some preliminary data that suggested there was infectivity during the preclinical

stage of the disease, but we wanted to know just when does it show up.

So we did this experiment. We inoculated a large cohort of hamsters. We're now repeating this in a variant CJD mouse model, and in the hamster model by oral inoculation. These were IC inoculations but they were at very low concentration, so we don't expect any carryover of the inoculum into the blood. And as you'll see, that is true. We have a data to support that now. And every three weeks we've sacrificed 20 animals, collect their blood, pool it, and then we'd inoculate 100 recipients with the pooled blood to obtain a titer by limiting dilution titration, and this is the results of these titrations. This is incubation time on the X axis, and these are the days at which the bloods were collected.

And what we see here is we had no infectivity in the blood 27 days after inoculation, even 51 days. But about halfway through the incubation period we start to see infectivity in the blood. It slowly increases as the infection progresses. Plotted on a bar graph here, this is what it looks like. These are our data points. And there is a curious thing about this which I have not come to grips with yet. I don't have an explanation for it. We know that the titer in this model increases geometrically over this same period. It goes up exponentially. This is a linear progression of titer in

blood. So it's not tightly linked to brain titer. We haven't done this in the same experiment. You know, I don't have the brain titers for this particular experiment, but we've done it in other experiments. And this is curious to me.

Preclinical blood titers, there's no infectivity. Just in summary, there's no infectivity during the first half of the incubation period. It increases linearly from that point. The infectivity must arise de novo because there was nothing there at these earlier time points. And the risk from blood increases with incubation time, but only linearly.

Now, I'm going to say a few things about risk reduction, and we'll finish with this. The classical methods of risk reduction, which you folks have been discussing all day here, are screening, deferrals and removal.

In terms of screening there's a lot of activity in this area, and we're part of it, but as yet there's no proof of principle even that PrP^{res} based assays will work in blood because no one has been able to demonstrate PrP^{res} that's the PrP amyloid in blood. Even though we know there's infectivity there, we can calculate from the amount of infectivity there that the PrP amyloid concentrations would be very low, about a picagram per ml, and you have to be able to detect that on a

background of 5 to 150 nanograms per ml of the normal protein, which is actually quite abundant in plasma.

There have been some incautious claims I think for detection. I just want to alert the members of this panel that it's actually quite easy to distinguish the blood from a clinically affected animal from a normal animal, because these animals are typically dehydrated and deteriorated, and you can tell when you do the draw that you're not getting a normal blood.

To the extent that a claim is made on this type of distinction, virtually anything will work. The challenge of course is to get a blood-based assay which will work on preclinical disease.

Deferrals are still largely based on the susceptible genotypes are deferred. The iatrogenic exposures are deferred, and within the last year or two we now have geographic exposures deferred as a means of protecting us from variant CJD.

These get rid of some of the risk and they're probably a good thing to do. I question this one right here, what we're getting for it. And my own feeling is our best hope is still removal strategies for these agents. There's not much of it in blood, and if we can devise a means to get rid of it or reduce it dramatically, I think it could have a lot bigger impact on our safety than this type of measure.

You're probably all familiar with this. Well, you probably haven't seen it presented this way, but this is a chart which Linda Chambers at the ARC put together, and the ARC was nice enough to give it to me. But this just shows you how complex the geographical deferral business is. It's gone through all these changes over time. I'm not sure just where we are in it at the moment. There are lots of conditions and variations.

And what do we get for it? Well, geographical deferral gets us one log of removal by design. It's 90 percent effective, it's 10 percent ineffective. My feeling is that if the reasons for which we put this deferral in place are correct, turn out to be correct, and an epidemic does materialize, we haven't done enough, and we'll be vilified for having not done enough. If there isn't an epidemic, we're all going to look like hysterics, and so it's really a no-win situation.

My own feeling is we need better modeling of the geographic deferrals. I'm not convinced that a 90 percent reduction, a one log reduction in exposure is meaningful in terms of a model which is postulating propagation of the infection through the blood supply, because it will eventually be overtaken by that 10 percent if something is actually happening.

I just wanted to finish up with something that's been kind of fun. Another thing that has happened in the

last year and a half is a fellow named Claudio Soto at Serono in Switzerland, showed that if you take and spike infected brain into normal brain, and then incubate it with moderate sonication over a 20- or 40-hour period, you can actually amplify the PrP amyloid in vitro or something that looks an awful lot like it. Well, the paper came out in Nature and we tried it the next day, and it worked the next day. I mean that's the first time anything like that has ever happened to me personally. It's not hard to do this. And the trick though was that they had been making claims that they were getting 100-fold amplification. When we put this on our--this was our starting material right here, zero time, and this is what it looks like after 26 hours. When we tried to quantitate this by fluorescence and other means we have in the lab, we were only getting somewhere between 4- and 8-fold amplification.

We invited the Soto Lab to come work with us, because they were interested in, as we were, in seeing whether we also got a amplification of infectivity at the same time, because if you do get an amplification of infectivity at the same time you're replicating this stuff, that is a proof of the prion hypothesis, and I'd have to put my skepticism aside. I'd hate to part with it, but I would in this case.

[Laughter.]

DR. ROWHER: I mean this is the kind of proof that I've been calling for for a decade. And so they did come to the lab. We discovered that actually we get exactly the same results, and I think they're actually over interpreting the amount of amplification they're getting, but the fact that you get any at all is quite remarkable.

And we have since put this on titration. What I told the lab is I wanted to have prepared 50 mls of this stuff so that we had plenty to characterize in the future if it does turn out to amplify infectivity. And we've done the titration both by endpoint dilution and limiting dilution titration, so we will be able to just discriminate an 8-fold difference easily but we can discriminate even down to a 2-fold difference in titer using these methods. And again, this could be a proof of the prion hypothesis.

Unfortunately, a lack of synthesis of infectivity would not disprove the prion hypothesis, but it would be curious that you could do this and obtain this stuff in so many different ways without getting infectivity.

Now, for the last several years I've been--finishing up with this slide, talking about loose ends in the blood-borne TSE story. One of these is gone now. There had been no unequivocal demonstration of blood-

borne TSE infectivity from natural infections. These transfusions in sheep I think eliminate that. We now know that this does happen in natural infections. We're still lacking a demonstration of blood-borne PrP amyloid in any infection, natural or experimental.

The work that I presented here that came from our lab, there were a lot of people who participated in this, and this is not even a complete list. And they're a bunch of very hard-working people, and I'll conclude there.

DR. BRECHER: Thank you, Bob.

We're running a little behind, maybe have time for one or two questions, comments. Keith?

DR. HOOTS: Just a comment. We spent yesterday gone through where this Committee had been, and I was looking back specifically to the issues that you were--in terms of recommendations that we made. In response to that discussion you alluded to about chronic wasting disease. And we did have a lot of discussion, and actually we did talk about trying to differentiate animal species in terms of developing the technology, and I think it does probably emphasize both what you told us at the time and what we may have feared and actually at least were cautious about, is that this was a reservoir that had significant potential to exacerbate, even though it seemed a fringe element at the time, and I think we

still have to keep that way up there now even more so than ever.

DR. ROWHER: I don't think any of us anticipated the ferocity with which this stuff was going to attack white-tailed deer, and white-tailed deer are--they have a universal range throughout North America, so there's really nothing now preventing the spread of this disease everywhere.

DR. BRECHER: I think we're going to take our lunch break now. It's almost 12:15. Why don't we come back at 1:15, and then we'll go to the FDA update, and then public comment, and then the discussion about the Committee members.

[Whereupon, at 12:13 p.m., there was a luncheon recess.]

A F T E R N O O N S E S S I O N

(1:18 p.m.)

DR. BRECHER: We're going to resume. We're going to begin with an update on the Blood Product Advisory Committee. We're going to have two speakers briefly discussing one, parvovirus B19 and then bacteria contamination.

Well, we have a few housekeeping items. Just one second. I'm sorry. Mac?

CAPTAIN McMURTRY: I would like for the Committee members to look at your calendars. I have tentative meeting dates for 2004. I have dates now only for January and August. You know we normally do one in the spring, and I don't have a spring date yet, but the winter date is January 15 and 16, and the summer date is August 26 and 27. So if you all will check your calendars to see if you have any horrible conflicts or know of any conflicts, and let me know before I start signing any contracts, I'd appreciate it.

Additionally, I finally have gotten the actual real charter over here. This one really is it. And I'll distribute that to you before the end of the day.

DR. BRECHER: Okay, you're up.

DR. NAKHASI: Thank you very much. I will be very brief I think since we know already we are late.

What I want to present today is the deliberations of the 75th Blood Advisory Committee Meeting, where we discussed one of the topics about the parvo B19 NAT for whole blood and source plasma. The issue basically was the FDA is taking a step-wise approach in resolving B19 NAT issues concerning whole blood and source plasma. At this meeting FDA sought advice on whether there is a risk of parvo B19 infection to transfusion recipients which is sufficient to warrant withholding high titer which is more than 10 to 6th genome equivalents per ml, cause the units of whole blood and its components from use.

The second question we were asked the advice on was whether there is a need to temporarily defer the high titer donors. And the third one was whether potential medical benefits to close contacts of B19 infected donors warrant notifying high titer donors. If so, also the subquestion was, what would be the time frame for notification?

A little bit of background about how we came to this, seeking this advice, because in September of 1999 BPAC advised that FDA should allow testing of plasma minipools for parvo B19 by NAT as in-process step to basically ensure viral inactivation process, such as solvent and detergent treatment of plasma and plasma

products, and to make sure the viral inactivation is complete, and not a donor screen.

So FDA has reviewed these NAT methods as analytical procedures with respect to sensitivity, specificity, and reproducibility under the licensed supplement for the manufactured product. That is the product, if there was a product made initially part of that, these tests would be part of that licensing product, not separately.

BPAC at that time did not recommend resolving the reactive pools to individual donors, nor did they ask them to identify the donor and donor defer. They did not recommend resolving the reactive pools.

Source plasma fractionators had been performing minipool tests on donated units at sensitivity sufficient to lower the viral load levels below the theoretical level of concern, that's 10 to the 4 genome equivalents per ml. This is basically set on--the level, this 10 to the 4 is basically a start that at that level there is enough neutralizing antibody in with the virus that will prevent infection.

What we have heard since then, that source plasma manufacturers are now resolving these reactive pools to single donations, even though the BPAC had recommended not to resolve single donation, they are resolving the single donations, rejecting the reactive

units, but are not notifying the donors or deferring them.

And also at that time, there was a proposal from the whole blood industry, which prepares the recovered plasma for further manufacture, and to provide transfusible components, would like to use the similar kind of strategy which the source plasma manufacturers are using. That is to detect high titer units and not to resolve initially to single units. So the strategy they would follow is two phase. Phase I is to identify the reactive minipools and reject the pools and do not notify the donor or defer the donor. Then they also wanted to go into the Phase II part of it which was to resolve the reactive pools to single donations now here, and reject the units, again, do not notify the donor or defer the donor.

So I think once we heard that, we had a BPAC in March of 2002 where we basically asked--we presented FDA's current thinking to the BPAC where we thought that once the individual donations are identified, it constitutes as a diagnostic. You know, identifying the donor means--constitutes medical diagnostics. And we also suggested that in the case of whole blood donations, they should go to the identifying individual donors prior to release of components, and units from reactive donors should not be used for transfusion. And also FDA's

current thinking was that also we should inform consent. Informed consent should be should be obtained from blood and plasma donors subject to site NAT testing.

At the Committee there was a lot of discussion basically to largely which was focused on apparent lack of medical benefits that might justify donor notification. So with that in mind, we then had a PHS Committee Meeting, where we discussed basically two issues. One, is identifying the donor, is it of medical benefit to the donor? Our second was, is it of medical benefit to the close contacts? So in the PHS Consensus Meeting we came up with consensus saying that it is not-- there's not enough information to suggest that it is medically beneficial to the donors. However, it could be beneficial for the close contacts.

So with that in mind, then we had this BPAC and we asked specific questions in the Blood Advisory Committee Meeting which was in December of 2002. The question was if donations of whole blood are tested for the presence of human parvovirus B19, are risks of transfusion recipients sufficient to warrant withholding high-titer positive units, which is again more than 10 to the 6th genome equivalents per ml from use for transfusion? And unanimously the Committee voted yes they should be, there is risk to transfusions to warrant withholding high titer.

However, there was a discordance in this whole process, but the Committee was not sure whether there was value established sufficient to warrant screening of whole blood for human parvovirus B19 for transfusion recipients. So in that, the Committee voted 9 no and 2 yes of saying that value has not been established to sufficiently warrant screening.

Then the second question, as I earlier mentioned was, is the temporary deferral of the positive donors warranted in the setting of following three settings. Whole blood donation, they said no because the rapid--the transient nature of the viremia. Also the quick immune response and by the time the blood donor comes back, by that time the infection would be resolved. So there is not necessary temporary deferral for the whole blood donations.

However, in the case of apheresis donations to make transfusion components, they felt, yes, there is a necessity to have a temporary donor deferral because they felt that apheresis units come quite frequently to donate and during that time the viral titer may not have gone down significantly, so it could be infectious.

Then they also, with source plasma donation they again said there's no temporary deferral necessary because of the same reasons which I earlier stated to whole blood donations.

And the third question was then, because we wanted to establish whether there was any medical benefit to contacts of parvovirus B19 infected donors which would warrant the notification of the positive donors. They felt, yes, because there is a potential--at least in the case of at-risk close contacts, for example, pregnant women, anemic patient, or immune suppressed persons, it has been shown that it could be fatal, it could be infectious and it could be dangerous for those people. So they felt that there is a medical benefit to contacts of the parvovirus B19 infected donors. So based on that, positive donors should be notified.

So the subquestion put to that was: if yes, what should be the time frame in which the testing should be done and notification should be done? So they felt that it should be several weeks because of the fact--again, the Committee was very, as you can see from the vote, very split in that, with 6 yes and no 4, that it should be done in a--if testing can be done in a shorter time frame, then only the donor notification is necessary.

So in summary, basically we felt that the source plasma industry appeals that, by the time they resolve the single donations, it is time beyond when it will have any benefit. So in source plasma settings, it will be a in-process control. However, with the whole blood

situation at this time, we still do not have yet the--because we do not know yet what the minimum level of infective is required. And so--and based on that, and based on that it takes eight weeks by the time people come back for donation, so it may be resolved, and the transient viremia situation, so that's where we are at the moment.

I guess I would like to end at that point. Thank you.

DR. BRECHER: Thank you. Any questions of comments? Jay?

DR. EPSTEIN: Yes. I think one of the things that emerged was a bit of a paradox. Data that were presented suggested that the model, that through notifying the donor we might achieve primary prevention of infections and contacts was really dispelled. We don't have a realistic prospect of that. That being said, evidence was presented that many of the more serious complications are still amenable to therapy much later in time, begging the question whether a delayed notification of the donor permitting delayed notification of a recently infected recipient might still have value.

Despite that, the Committee largely voted that there would not be a value to the notification in this situation in which donor notification would be significantly delayed, and so I think that there was a

little bit of disconnect between what we learned at the meeting and how to votes came out. Nonetheless, I think that the positive message was that if there's the ability to remove transfusible units, that that's worthwhile, and that the greatest opportunity to do that was with apheresis models. And I think that the FDA was advised that recommendations and potential requirements to move the parvovirus screen forward as a formal donor screen are probably not supported by the evidence of a benefit. So our current thinking is not to move toward the, if you will, real-time test or up-front screen requirement.

DR. BIANCO: I wanted just to ask a quick question of Hira and Jay. So the fact that you, as you said, that you are not moving towards donor screening, does that mean FDA would be supportive of a new process approach by the whole blood sector?

DR. NAKHASI: Go ahead.

DR. EPSTEIN: Well, I think what it means is that we would probably regard the testing as voluntary, but that we might issue guidance on what do you do if you've done a voluntary test and you have a positive result? So in a certain way that's more flexible yet, because in some scenarios it may resemble screening, and in other scenarios it may only be testing of outdated recovered plasma. So I think that if we allow it to be voluntary, then there will be a set of different

practices, but that we may have ultimately guidance on how to manage units and donors in the face of a voluntary test.

DR. BRECHER: Other questions or comments?

[No response.]

DR. BRECHER: If not, thank you. We'll move on to the summary of bacteria and the BPAC, and Jay is going to be presenting that.

DR. EPSTEIN: I apologize. I have no slides. We had another person preparing a presentation who unfortunately could not be here today, so I'm going to pinch hit.

I'm going to summarize the discussions that transpired regarding approaches to control bacterial contamination of transfusible components, also from the same most recent meeting of the Blood Products Advisory Committee on December 12, 2002.

The discussion was opened with a summary on the significance of bacterial contamination, and the candidate detection, and other intervention methodologies. Mark Brecher has already comprehensively reviewed this at this meeting, and I'll just simply flag that there's a generally accepted figure that with state of the art procedural controls, contamination rates of the order of 1 per 1,000 to 1 per 2,000 of platelet units will occur, that the sources of contamination include

bacteria on the skin surface, skin plugs that are cored out by the needle which then may contain bacteria in the deeper parts of the skin tissue such as follicles and glands, and occult bacteremias in the donor who presents as asymptomatic, and then perhaps least commonly, environmental contamination of the collection system.

Now, the methods that were reviewed included the culture, the urine dipstick, the pH, the gram stain, the swirl test for the platelet, nucleic acid detection, automated culture. And then we talked also about the effectiveness of arm preparation, a diversion pouch, and the whole concept of a quality control versus pre-release screen. So again we've already heard many of the details and I won't elaborate on those.

We then provided an update, where we were with the diversion pouch, which had been discussed at a previous meeting of the Blood Products Advisory Committee. Dr. Vostell [ph] and our group reviewed the data, which were again summarized here today, on the reduction of contamination in units for which the initial collection volume generally of the order of 20 to 30 mls, has been diverted. And the conclusion from the previous Blood Products Advisory Committee, that those data were not in and of themselves sufficient to be a basis for licensing claims or approval claims for devices for reduction of the frequency of bacterial contamination of

units, but that nonetheless, FDA would proceed to approve diversion pouches which met the mechanical characteristics. In other words, that they would have a unidirectional flow, you know, no back flow, and that they would collect sufficient volume, and that the process didn't interfere with the collection otherwise, and that they maintain the closed system.

So we have in fact received a number of submissions for collection systems, including diversion pouches, and they're under review, and it would be our intention to approve them as alternative collection systems without necessarily them being specifically labeled for reducing bacterial contamination. Further validation could come later, and that would be fine, but the products will become available on the market.

We then moved to a discussion of several issues. First is the question, whether the FDA ought to respond to the AABB proposed standard to prefer the modified arm preparation, using 70 percent isopropyl alcohol followed by 2 percent tincture of iodine above the current povidone iodine procedure. And of course the studies already mentioned were reviewed, which showed an apparent benefit of substituting that modified procedure which, as has been noted, is now in use in a number of countries such as the U.K. However, on critical review of really the world's literature on the subject, a number of papers

were discussed which failed to show any statistically significant difference between those two procedures or indeed a third alternative procedure using alcohol alone, and probably the most compelling of these was a paper that compared the frequency of a positive blood culture in the hospital setting, based on the different arm prep, and there was simply no statistically significant difference. The only difference that was found was with the use of green soap, which certainly should be abandoned in any setting of blood bank phlebotomy.

So the conclusion--well, I'll come to the voting--but the analysis there did suggest that the case based on the two published papers is not compelling. The Committee was then asked whether available scientific data support preferential use of isopropanol/tincture of iodine procedure for the preparation of the donor phlebotomy site, compared with the current standard procedure based on povidone iodine preparation. And the voting was 6 votes in favor, 7 votes against, without abstention, and the nonvoting industry representative indicated that he tended to agree with the yes vote, effectively giving us a split vote.

And I think that our current thinking within the Agency is that we don't think that the data set is strong enough for us to make it a regulatory requirement to

implement the modified procedure. However, we would not impose an AABB voluntary standard.

We then approached a second set of issues that are actually somewhat linked. Dr. Williams described the quality control approach for detection of bacterial contamination that FDA is seeking to recommend. He discussed also the linkage to the question whether one can take a quality assurance sample by sterile connection and still have the product in storage for its usual outdate. The question then of the level of sterility achieved with sterile connection devices was then focused on in the light of a recent European report of a rather high rate of bacterial contaminations with the use of these sterile welds. However, data were brought forth both by Jim AuBuchon, based on studies done at Dartmouth, and also by the manufacturer, Truman(?) Medical Corporation, which established that there is in fact a very high level of reproducibility of the sterile weld, that in the cases where the weld is unsuccessful, the leakage is obvious if one simply looks, and that for welds that have not visibly leaked, the contamination rates are extremely low.

So the Committee was then asked a couple of questions. First of all, with respect to the sterile weld, they were asked: do the available data on sterility of the sterile connecting device procedure

support the use of this procedure to collect samples for bacterial detection from indate platelet products? And the votes were 13 in the affirmative, none negative and no abstentions, and the industry representative agreed with the affirmative vote. So that was unanimous in favor of the reliability of the sterile connector, which then makes it available to be used as a sampling method within the shelf life of the product.

The proposal on statistical quality control focused on encouraging the use of validated methods to rule out contamination rates greater than 0.2 percent, and one particular method was suggested based on certain numbers of periodic cultures over time. The Committee then was asked whether it concurred with FDA's proposed statistical approach to providing quality control for platelet contamination. In this case there were zero votes in the affirmative, 11 votes in the negative, and 2 abstentions, the nonvoting industry representative indicating agreement with the abstentions. The significant comments from the committee discussion focused on the concern that the medical benefit of a statistical quality assurance approach to monitoring platelet contamination has not been validated in any suitable large-scale study, and that therefore we were advised that we should be shy of promulgating such a recommendation, which after all, represents quite a lot

of investment, is short of what people really want which is a release criterion assuring a sterile product or at least a product culture negative at the time of issue, and that there was a lot of concern about the specifics of a particular statistical approach, whether it went far enough.

And then the third issue that was brought forward concerned efforts to design clinical trials to validate the clearance of devices intended for the screening of platelet products prior to transfusion. And a design, a specific design was proposed to evaluate automated bacterial culture devices for the screening of platelets, and to at the same time validate the shelf life of a 7-day versus a 5-day platelet, coupling the extension of dating with an antecedent culture.

The Committee was then asked whether it concurred that the data derived from FDA's proposed clinical trial design in concept would be appropriate to support the clearance of devices for pre-release screening of platelet products for transfusion, and there were 13 votes in the affirmative, no votes in the negative, and no abstentions. The industry representative agreed with the affirmative vote. The Committee did however comment that such studies possibly would have to be both very large and very costly, and that they emphasized that they would like to see data

supporting the 7-day dating of platelets, and encourage some flexibility and implementation of a 5- versus a 7-day platelet.

There were a number of--I didn't mention--presentations in the open public hearing, representing both industry, the product manufacturers' blood collection establishments and hospitals.

So the FDA has not yet followed with any policy statements in these areas, but I think that the message that we've received stay neutral on the revised arm prep go ahead and approve diversion pouches as alternative collection systems, and back off a little bit and do some scrutiny of the value of quality control procedures, and by all means encourage and go forward with studies that would support approval of devices for pre-release bacterial screening of the platelet product with or without extension of platelet dating.

So that's where we are.

DR. BRECHER: Thank you, Jay. Comments or questions for Jay?

[No response.]

DR. BRECHER: Jay, could you maybe comment on how big a study might be needed?

DR. EPSTEIN: Well, I think two factors govern that. One is the belt line. If basically the boss test or standard is the culture at issue or outdate, what is

the necessary denominator to adequately measure the sensitivity of the up-front culture? Now, statisticians can give you numbers, and there will be confidence bounds based on any given denominator. The question is: what would be sufficient? I think something in the neighborhood of 50 to 100 positives detected in the real world would give us a pretty good assessment of the up-front culture, although it would probably not meet a lot of statistical rigor. In other words, when you applied statistics, you'd get a confidence interval, it would be wide. But for instance if you had only one failure out of 50, I think it would give us fair confidence that the up-front culture is in fact pretty good.

Then the question is: well, what's the expected frequency in the study? Because that will then drive the study because you want to try to achieve the necessary denominator. And a little bit that depends where you go. If you have centers that are achieving contamination rates of .5 percent or less, then it's going to take you a very long time. If you have centers that unfortunately are only achieving rates of 1 or 2 percent contamination, then it doesn't take very long or large numbers. So assuming that the studies are only done in the state-of-the-art centers, then you're talking about rates of about 1 in 1,000, and so I think you're talking about something in the ballpark of 50,000 samples done prospectively in

order to target a denominator of the order of 50, which I think is sort of a bare bones minimum to say anything remotely statistically meaningful. But I think that numbers like that are achievable if there were a concerted effort to do this in a multi-center study. And as I said earlier, with the candidate AABB standard calling for routine use of culture, even if that's done in the quote, unquote, "quality control mode" as an up-front culture, the system as a whole has the opportunity to do some endpoint culturing of a subset which will then give us the answer.

So, a large number of centers are going to be doing it up front, and we need only some of them to do the outcome culture, and then we'll get our answer. So I think that's back of the envelope, and what we would do is respond to a specific proposal. But I think that those are credible numbers.

DR. BRECHER: And will they have to be outdated platelets or would you take an issue culture?

DR. EPSTEIN: Well, I think that the concept is that you want to know what it predicts in the real world, and one of two things happens. Either you issue the platelet and your interest is to know what was true at time of issue, or you don't issue the platelet and you can gain scientific information by culturing the product you would otherwise discard. In fact, the culture at

outdate is the more powerful of the two tests because it gives all the slow-growing organisms a chance to replicate. But I think that we certainly could accept a study that contained both of those endpoint measures.

DR. BRECHER: Thank you, Jay.

DR. EPSTEIN: Let me just say that if the study includes the 7-day outdate, it would be important to make sure that a significant subset included culture at day 7 because there is the concern that you might have with the up-front culture detected all the rapid growers, and by extension of dating, allow the possibility for a new era of slower-growing organisms to become the lead issue. So we would want to make sure we didn't miss that.

DR. BRECHER: So clearly outdate or say 7-day platelets would be the optimal design. I take it aerobic cultures would be sufficient. We wouldn't have to do anaerobic?

DR. EPSTEIN: Again, this is a debatable point. As you well know, the two systems approved for quality control bacterial testing differ in that one system has anaerobic bottles and the other does not have an anaerobic system. However, the evidence is that the vast majority of significant infections are with the aerobes or at least facultative anaerobes and would be detected in the aerobic system. So I think that's a discussion item. At this point in time I wouldn't preclude a study

that studied only aerobes and facultated anaerobes, but I think we want to be sure we're doing the right thing there.

DR. BRECHER: Questions, comments? No question about automation, Celso? No?

DR. BIANCO: You asked all the questions.

DR. BRECHER: All right. Then this concludes the presentation portion of the meeting. The floor is now open to public comment. Oh, one--

DR. NAKHASI: I just wanted to remind people, because I think Jay mentioned earlier, to remind people that we are having a Blood Advisory Committee Meeting on March 13th, where we will be discussing West Nile virus update. And the purpose of this update is to really bring up to speed what is happening with the industry folks with regard to testing. As you heard yesterday, testing should start in beginning of summer, so we'll be hearing from the update from the industry, how far they have reached in the tests and seroprevalence studies, and also from other people. So I think I just want to remind that we have that West Nile virus on the workshop. It will be an informational session.

CAPTAIN SNYDER: Where is that?

DR. NAKHASI: Blood Advisory Committee Meeting, where it is, I think I don't know. You will get a notice. You will get a prior notice.

DR. BIANCO: Hyatt, Gaithersburg.

DR. BRECHER: So we're not open to public comment. If someone has a public comment, they can approach the microphone, identify who they are, and who they represent if they represent a group, and I'd ask that people not read too long a written kind of--we can certainly put something into the minute if they could just hit the highlights of what it is they want to discuss.

MS. DeSIMONE: Thank you, Mr. Chairman. My name is Anna DeSimone. I'm the past president of the Hemophilia Association of New Jersey. My son, Max, is a child with hemophilia.

And as you know, persons with hemophilia rely on clotting factor replacement. As a consumer I'm pleased the Secretary and Dr. Slater find the work of this Committee valuable enough to continue its existence. It's such an important forum. I'm especially encouraged, Mr. Chairman, that you chose to review the events which brought about the creation of this Committee, the HIV blood crisis and the IOM report.

Listening to the information at this meeting, two themes resonate profoundly for me. The first is conflict of interest among experts. Expertise does not exist within a vacuum, and in the summary from the IOM report, I quote, "One of the difficulties with using

experts to give advice is the interconnections that experts accumulate during their careers. As a result, an expert may have a history of relationships that raise concerns about whether he or she can be truly impartial when advising a course of action in a complex situation."

And the second theme is the public's perception of blood safety. With all due respect to Dr. AuBuchon, the media is not responsible for the public's distrust regarding the safety of the blood supply. Look at the history. The public is distrusting because of the insensitive response patients received when there was ample information, knowledge and technology available to improve the safety of blood and blood product. This technology at the time was not deemed cost effective. We in the hemophilia community were told there was a statistically negligible risk of contracting HIV from clotting factor. There are thousands of people in our community for whom a statistically negligible risk became a death knoll.

Thank you very much.

DR. BRECHER: Thank you.

MS. GREGORY: I'm Kay Gregory, Director of Regulatory Affairs for the AABB. This meeting I think has been very good. We've heard a number of issues that we've all been struggling with. I congratulate the Committee on the thoroughness of the review.

But I'm here to mention a couple of other things that need to be considered any time we're going to talk about priorities for blood banks and what they should be doing.

The first of these really has to do with donor screening initiatives or donor questioning, donor interviews. And this Committee hasn't heard a lot of about it. Some of the other committees have. But the AABB does have an inter-organizational task force working on a uniform donor history questionnaire. It's really a cooperative effort of all the blood agencies as well as the FDA and the CDC, and we have developed a streamlined questionnaire for donors. We hope it will make our donors a little happier. We've also worked on an abbreviated questionnaire, educational materials that will be standardized, a medication deferral list, and then finally, a user brochure that describes how the blood centers could be expected to use each of these materials. And I think this is an important initiative because this is really the first time ever that there has been an attempt to find out whether the donors actually comprehend what we're asking them.

We did this in a couple of ways, by doing focus groups, and also by doing cognitive interviewing that was done by the National Center for Health Statistics.

The second thing is, we're going to be talking about resources and how much money does it take to do everything. This particular project was done on a very shoestring budget. The only money we were able to get from anyone was a grant from NHLBI. And George, I'm sorry, I've forgotten the amount. I think it was $80,000 to get the cognitive interviewing done.

The reason I'm mentioning it now is this really needs to be an ongoing project. It's not something that you do once and then forget about. There are always new donor questions that we're considering adding, and we need to continue the evaluation of the questions, at least to see if the donors comprehend them. And in the future I can see that the next step is going to be to develop these questionnaires so that they're useful for computer-assisted self interviews and probably with audio components involved. So in any prioritization of what blood banks are going to be doing, we need to remember that this has got to be a big change for blood centers, and this needs to be included in their prioritization list.

And then finally of the projects that's been dragging on and on and on, and I know Mike wishes that we would get it finished, and that is to change ISVT 128 bar coding for all of our blood products. One of the major advantages of that is that it does allow you to track

your units much more carefully in that it will do away with duplicate numbers. So if I'm a transfusion center and I get blood in from two different collection facilities, I will not longer get two units that may have the exact same identification number on it. So while these may not be directly related to transfusion transmitted diseases, as some of the things you've been discussing today, I think they do need to be included any time you're making a priority list of what things should be addressed in blood banks.

Thank you.

MR. VOGEL: Mr. Chairman, Committee members, my name is Rich Vogel, and I'm a member of the Hemophilia Association of New Jersey and immediate past president of the Hemophilia Federation of America. More importantly, I'm a consumer of blood products, having severe hemophilia.

I've found the past few days' presentations very informative and, for me, very appropriate. I've been HIV positive for over 20 years and probably hepatitis C as long, both courtesy of blood products. If that's not enough, I recently acquired Parvo B19 virus and Lyme disease, both at the same time. So, as I say, the past few days have been very interesting.

With resurgence of HIV in the general population, especially with the younger generation, it

would seem now would not be the time to feel that there is little or no risk of HIV in the blood supply and to eliminate new technologies such as NAT testing.

By definition, transfusion medicine is that multidisciplinary branch of medicine that focuses on all of the available medical, scientific and technical information applicable to the benefit of patients receiving all blood products or related materials produced by molecular biology or biotechnological techniques.

Those engaged in the practice of transfusion medicine have the responsibility of integrating the various concepts, techniques and other elements of relevant knowledge from the various contributing disciplines, such as clinical medicine, epidemiology, hematology, stem-cell biology, immunology, microbiology, molecular genetics, protein chemistry, transplantation, immunobiology, as well as health research methodology.

Blood banking and the manufacturers of blood products have historically been relatively outside the influence of regulatory authorities. This all changed wt the transmission of HIV in the blood products. The blood banking industry has embraced, although not too enthusiastically, the principles of systematic quality management and good manufacturing practices.

It is well known that many adverse reactions associated with transfusion of platelets and red blood cell units are caused by the unwanted passenger in these products--the donor leukocyte. The past decade has seen a significant improvement of technology in the removal of leukocytes from blood products, and reports of the potential benefits of leukoreduction have continued to accrue, yet some issues remain controversial, most importantly, cost-effectiveness.

Another issue this Committee spent time on was the HIV-Hep C lookback. The New South Wales Division of the Australian Red Cross blood services implemented a very successful HIV lookback, establishing and maintaining an observational database. This database was an integral part of several research projects that contributed significantly to understanding HIV pathogens.

The information obtained can then be used to describe the natural history of transfusion-transmitted infectious diseases and disease pathogens. Worthwhile, indeed, yet the controversy here, once again, became cost-effectiveness.

We, in the hemophilia community, would urge this committee to continue with their excellent recommendations and to look beyond the cost-effectiveness and adopt to recommend the use of NAT testing across the

board and to continue to make the blood supply and blood products as safe as possible.

As experts, society puts their trust in you to make proper, life-saving decisions for all. Don't let them down. In the words of the great philosopher, Mr. Spock, the needs out of the many outweigh the needs of the one.

Thank you.

DR. BRECHER: Thank you.

It's interesting to have heard from all of these experts and authorities. It reminds me of I think it was something, if I can paraphrase what Albert Einstein once said, he always had a little bit of contempt and disrespect for authority, and it was God's revenge that he made him an authority.

[Laughter.]

DR. BRECHER: We're now moving into the session where the Committee will discuss what recommendations it would make, and we're open to recommendations.

Mark?

MR. SKINNER: Mr. Chairman, I mentioned yesterday morning, and I do have copies of a resolution that I would like to put forward, relative to the use of recombinant products, and what we're seeing is occurring around the country. I think the resolution is pretty straightforward. It's available on a disk if the folks

want to put it up on the screen, if there's not enough copies for the group.

Basically, what it does is it has five "whereas" clauses that simply recite some facts; the first of which is a reference to the CMS manual, which uses outdated terminology, referencing the old heat-treated and nonheat-treated products, restating verbatim the two previous recommendations of the Committee on the use of recombinant products, acknowledging that the leading medical and scientific body that makes recommendations on hemophilia care, MASAC, has adopted these recommendations.

And then, lastly, part of which is leading to this recommendation, is information that was available to MASAC at their last meeting, where they've taken note of a pushback on the use of recombinant factor, particularly in light of patients who altruistically agreed to change back to plasma-based products and now are wanting to go back to recombinant products, that there's been some resistance on the part of at least one insurer, and now the trend that we're seeing, in light of state budget constraints to resist allowing patients to remain on recombinant products.

So what I'm simply asking is that the committee reaffirm its previous statements without change and that it elaborate on the one previous statement, where it

talked about removing impediments to insurance, access for recombinant products by simply asking the secretary to work with Medicare to update their guideline to remove the outdated terminology, which is inappropriately being used to restrict the use of recombinant products.

I would move adoption of the resolution.

DR. BRECHER: We're going to get the wording up on the screen in just a second.

The Committee members have copies in front of them. Suggestions, comments, word changes?

Let's just pause here for a second until we get it up on the screen.

[Pause.]

DR. BRECHER: Jay?

DR. EPSTEIN: Mark, could I just ask you to explain a little bit how does the current terminology interfere with the reimbursement?

MR. SKINNER: And I do want to distinguish between this is not a discussion of reimbursement levels, which is a separate discussion that's occurring. This really is a discussion of speaking of access to the products, and there has been confusion, and we've heard it either through the reimbursement specialists of the providers of the products, that by speaking to heat-treated and nonheat-treated varieties, when we're actually now talking about newer generations that didn't

exist at the time that these products were developed, that the lack of the terminology of recombinant in those guidelines is leading people to believe that it's acceptable or that there is not an obligation or it's not important that they include recombinant as an available product for the doctor and the consumer to choose from.

DR. BRECHER: Jean?

DR. LINDEN: I have a similar concern and question. I mean, there's reference here to the provisions being a problem, but we have not been shown the provisions, so I don't think I can conclude that the provisions are a problem. All there is that there's outdated nomenclature.

MR. SKINNER: I actually do have the full text of the language here, which I would be happy to read. I did footnote a reference, so it's fully documented in terms of actually what it is.

There really is one paragraph that is relevant. This is from the carriers manual. It has a general section, then it has a reimbursement section, and then what the language is to which I'm referring--pardon me, if I paraphrased it inappropriately--is:

"Reimbursement is based upon the least-expensive, medically necessary blood-clotting factor. The blood-clotting factors are available both in a heat-treated variety and a nonheat-treated variety. The Food

and Drug Administration has determined that both varieties are safe and effective. Therefore, unless the prescription specifically calls for the heat-treated variety, reimbursement is based on the least-expensive, nonheat-treated variety," and then it goes on to talk about billing practices and frequency of use.

DR. BRECHER: Mark, just to clarify, this is from one state?

MR. SKINNER: No, this is, I believe, from the CMS guidelines that they provide to carriers for use in reimbursement.

DR. BRECHER: Celso?

DR. BIANCO: Mark, I will express very much my feeling here. I think that, in principle, in my position, I feel that people being treated for hemophilia should have access to recombinant products, and if this was the resolution, and reaffirming previous resolutions of this Committee, I would feel very comfortable to say so.

When you put all of these legalities and all of these issues, I know even asking the regulators, Dr. Epstein or Dr. Linden, about that, and I think that we have to urge the Secretary to continue following that in terms of removing the barriers, whatever barriers they find.

So I would suggest that these be reduced, at least for my comfort, to maybe a paragraph.

MR. SKINNER: I guess what I would say in response, and I understand your concern, is that as we looked at, yesterday morning, and received the report of where things have been, we, in fact, it was noted, at least in the first draft, that great success had been made in transition to recombinant, but it also went on to talk about insurance barriers.

As we identify specific items that have not been addressed, I view this as really following up on what we've already said. We've identified a specific insurance barrier that's within the purview of the federal government that this Committee can make a recommendation on.

So what we're really talking about are activities to achieve the goal and directing the Secretary's attention to a specific item, simply reaffirming what we've said before, that's already on the books, and now we can offer some guidance that can make a real difference in a very timely fashion.

DR. BIANCO: Yes, but the role that I see for this Committee is the big policy picture; it's not picking here and there from the bureaucracy, where the obstacles are. I think that if this Committee provides the overarching support, that is, for the hemophilia

organizations and physicians treating hemophilia, hemophilia treatment centers, to go after and say, look, the Blood Safety and Availability Committee made that resolution and made that recommendation to the Secretary, we'd want to follow up. Those are the specifics.

MR. HEALEY: Mark? I'd just like to say I think, Celso, that's exactly what this recommendation is trying to do. If this Committee does embrace this and resolve the document that's been presented here, this is a tool that those hemophilia treatment centers, that those doctors, that all of those people you just listed, can then use to make sure that adequate reimbursement is put in place to make sure that the appropriate language is changed.

So I think the request here, and our action, will result in a tool that can be used to effectuate exactly what it is you said our ultimate responsibility is.

MR. WALSH: Mr. Chairman, a different consumer perspective is, is that timing is of the essence here, and there are state Medicaid offices making determinations right now about what access to therapy individuals with hemophilia have.

I think it's extremely important that we break through the potential bureaucratic delays in interpreting what we're asking for and speak directly to the point,

and I would certainly embrace this and would welcome an opportunity to second this motion.

DR. CHAMBERLAND: I'm obviously not a voting member of the Committee, so I guess I'm sort of reacting to this generically in that, while it's definitely true that this issue has come up in previous meetings, my recall is that this has been in the context of when there was more discussion and presentation of information about this in the meeting, and I guess I just am concerned because I just don't think that there's been a presentation, a more fuller presentation, of information about this. CMS is not even here at the table.

So I'm just, as I said, I'm just reacting to this sort of generically as to how the Committee usually handles issues that are brought before it to deliberate, discuss and vote upon. Maybe this is something that should be more fully examined on a future agenda, whatever. But as I said, as a nonvoting member, it's just kind of an observation about this.

DR. BRECHER: Keith?

DR. HOOTS: I understand that perspective, Mary. I'm concerned about the exigency that Mark alluded to. I mean, there clearly are incidences where states, employing the language or at least alluding to the language that Mark has stipulated here, have made a quantum leap to their own Medicaid coverage programs by

denying both children and adults access to recombinant Factor VIII.

So I'm concerned that a long scrutiny of this whole issue, particularly as it relates to language of very outdated and arcane former HCFA language, would unnecessarily delay the consideration.

DR. KUHN: I wanted to say, personally, that I have been at least in consultation with some of these state Medicaid offices in which they are using this manual I guess as their authority to continue to use antiquated, I guess, treatment, and by doing so they're setting up a barrier, whereby people or patients cannot have access to the recombinant.

And I believe that it's time that we move or help the CMS move toward a 20th century perspective, especially in light of the recommendations that we have made. I just believe that these probably have not been filtered down. They probably have been filtered down verbally, but since they have not been in writing, and they still are using an old manual, they are still looking at hemophilia treatment as it was in the early '80s, and they're not looking at it as in light of recombinant technology.

So I really believe that this is a good and a timely recommendation which is very important for access to recombinant therapies for people with hemophilia.

DR. BRECHER: John?

DR. PENNER: We've visited this situation before extensively. I think we've covered it all. CMS is not here, but they frequently don't show up anyway, and as far as I'm concerned, I think we ought to proceed with something that we have sufficient knowledge for, and I would call the question.

DR. BRECHER: I suggest a compromise that we have suggested using in the past, in that since this is somewhat off the topic specifically of this particular meeting, I think that it's an important issue that can be conveyed to the assistant secretary in the form of a letter from the Chair that Mark and I can work on and that can be made public, but I don't think it needs to be an official recommendation from this particular meeting. Would that be an agreeable option?

MR. SKINNER: I actually would prefer to have the official mark of the Committee. I think to get the notice of what's actually occurring in a very timely fashion, and I don't want to force this to a vote at my own jeopardy, I mean, I would be curious what others thought as well, but knowing that most state legislatures have begun, that the budget, that 49 of the 50 states are running a deficit, and Wyoming, the only one that says they aren't, is probably in denial.

This is an issue that a lot of states are going to be grappling with, trying to figure out how to manage their budgets, and this is four square in front of them. We've heard anecdotes now out of at least four states, if not more, in terms of hemophilia being the target for cutbacks in the state budgets.

We're at the very beginning of the legislative cycles, and they're going to move rapidly, and I think a strong statement--I really view this as an extension, and a clarification, and interpretation of our work. I really view this as no new policy change. It's simply trying to reinforce, in the strongest way possible, and I think a vote of the Committee is the way to achieve that.

DR. BRECHER: How about an alternative compromise, just to keep it simple and short. If we go down to the third paragraph of this document, if we "reaffirm that every effort should be made to make recombinant clotting factors available to all who would benefit from them, and all barriers..." and insert a parenthetical statement, "including the use of old terminology," closed parenthesis, "...to conversion from human recombinant clotting factors should be removed."

It's short and simple. I think it gets to the point that you want to address. Would that be more acceptable to the Committee? We have three choices:

We have the choice of writing a letter from the Chair, in conjunction with a subcommittee that can be delegated of this Committee. My sense is that the Committee does not want to do that.

Why don't we just take a vote of voting members, who would prefer that we do that?

[Show of hands.]

DR. BRECHER: All opposed?

[Show of hands.]

DR. BRECHER: So we're not going to do that.

A second option is to go with this shorter reaffirmation, with the insertion of just a few words about terminology, which seems to be the biggest problem.

Voting members, who would favor--

DR. PENNER: Can you please ask the proposer?

DR. BRECHER: I'm sorry, we need it to be proposed.

MR. SKINNER: I would have to say this resolution is a collective work product of a number of people offering input, and if some who are closer to it, to some of these individual instances than me, believe that would give sufficient weight to carry the message, then I would defer. My sense is it does not; that having a full restatement that puts in one place so now we have a physical document that we can show in context of the

whole linear discussion that's occurred by this Committee and others around it, I think would be the strongest.

DR. BRECHER: Mark, I would see that as the third option that we would vote on.

MR. SKINNER: So I guess my preference still is the original, unless my colleagues tell me that I am overzealous in my pursuit of the resolution.

DR. BRECHER: Fair enough. We're not going to write a letter. We're going to do one of these two things, either a truncated version or the full version.

All in favor of the truncated version?

I'm sorry, Jean?

DR. LINDEN: Can you please clarify exactly what's in the truncated version; it's the third paragraph and the last paragraph or what?

DR. BRECHER: Let me write it on the screen.

[Pause.]

DR. BRECHER: This is the truncated terminology that I have proposed. "The Advisory Committee, wishes to reaffirm its previous recommendation regarding recombinant clotting factors." No, that's not it. Where did it go on the page? Go down a bit.

[Pause.]

DR. BRECHER: "We reaffirm that every effort should be made to make recombinant clotting factors available to all who would benefit from them and all

barriers, including the use of outdated terminology, to conversion from human recombinant clotting factors--"

DR. BIANCO: Mark? Celso.

DR. BRECHER: Yes, Celso?

DR. BIANCO: I would add the word "including the current use of outdated terminology" to just emphasize that this is the--

DR. BRECHER: We could do that.

Any other suggestions?

[No response.]

DR. BRECHER: So this would be the shorter version. So this is option two. Option three would be this longer version.

MR. SKINNER: If I could just ask a question of process. So the process would be to take an up or down vote on this. If it was voted down, then we would go back to the original motion and have an up or down vote on it?

DR. BRECHER: Correct.

DR. GOMPERTS: I would be comfortable with it, but do believe that the two first paragraphs of the original statement, the linking with CMS to Medicare coverage decisions and policies of state Medicaid agencies, I think that those are relevant.

DR. BRECHER: I've lost my copy. Can I look at your copy? I've lost my copy.

[Pause.]

DR. BRECHER: So what's the Committee's sentiment? Should we include those first two paragraphs in the shorter version or not?

DR. PENNER: I think they're pertinent, too. I quite agree. It really provides an emphasis.

MR. HEALEY: I think by the time you add the first two paragraphs, you're pretty much back to the original as it is, and I think there might be support for that.

DR. BRECHER: Yes?

DR. HAAS: May I recommend the voting strategy that we vote on the original proposal, and then if that doesn't work, go to an amended one? That would seem to me to be a little more in the flow of the way things are done.

DR. BRECHER: We can do that. That's a good suggestion.

All of those in favor of the full proposal, voting members?

[Show of hands.]

DR. BRECHER: Ten.

All of those opposed?

[Show of hands.]

DR. BRECHER: So it's 10 to 3.

CAPTAIN McMURTRY: Can I see the nay votes again?

[Show of hands.]

DR. BRECHER: So the full motion will carry. We will insert that.

DR. EPSTEIN: Can you just read the vote?

DR. BRECHER: I'm sorry? It's 10 for the full language of this recommendation and 3 were opposed. So we'll accept this resolution.

New resolutions?

DR. DAVEY: Mark?

DR. BRECHER: Yes, Rick?

DR. DAVEY: I wonder, before we get into proposing resolutions, if the Committee would like to discuss a little bit about how we're going to approach prioritization? I mean, that is the topic of the day, and just based on the discussion of yesterday, which I think we all found interesting from our ethicist colleague, I would propose we talk a little bit about the framework that we're going to use for prioritization, the bigger picture, if you will.

Just a couple of thoughts that I have. It appears to me that we wrestle always on this Committee between the bigger picture of doing all we can for the individual, meaning that we do everything to prevent one case of a disease, one extreme. Perhaps, with the other

extreme, we put great weight on what we might call resource allocation and donor issues and supply, and there's a continuum.

We all, maybe individually, we might come down in different places on that continuum, but it's a bigger picture weighing the individual against societal issues of resource allocations and blood supply that I think we wrestle with.

I would like to think the interesting range of transfusion-transmitted diseases that we discussed over the past two days, that we could almost begin to prioritize what are key to protect the individual. I think we all would agree that HIV minipool, perhaps bacterial detection, might be on that extreme. While, perhaps on the other end of the list, which could be considered to be eliminated in the interests of resource allocation, we might look at, obviously, p24 antigen, which is already on the skids to perhaps leave us, but maybe syphilis testing. Some of us might want to consider the European vCJD ban on that end of the spectrum.

But I think I'd like to open the discussion a little bit to how we're going to draft some resolutions in the context of this bigger picture of prioritization.

DR. BRECHER: Jay?

DR. EPSTEIN: I would just like to comment that the context of prioritization is conditioned by the real-world environment. What I mean to say is that there is sort of a mixture of what can be proactive and what can be reactive. For example, some things present themselves as opportunities because the technologies exist, and then the problem is moving the system to use them. Other things are problems that we know need solving, and some of those fall into bins where there are resources and others fall into bins where there aren't resources.

I guess my concern from all of this is that, whereas, it's important to talk about priorities, I think that we have to also talk about how decisions are made to allocate resources; you know, what is it that we need to do to move the system in a given direction, at a given time, on a given issue? Because I guess my concern in the end is, you know, a lot of people generate a lot of lists, but then there's frustration about things that didn't happen, and so what sense does it make to just talk about the list?

DR. BRECHER: Yes, I agree with you, Jay. I think there's been a lot of frustration not only of generating lists, but the resources that are being allocated are not where some people think they should be allocated, and the question I think to this Committee is how do we do a, if we're not doing a good job, which may

be an assumption, how do we do a better job of allocating resources to where they need to go?

Chris?

MR. HEALEY: Doesn't that really kind of depend on two factors? I mean, first is what are the risks? What are the health threats to the blood supply? And then, secondly, I think you said it, Jay, what are the opportunities to impact those? Your top priority might be bacterial contamination, but if you don't have any means to impact that, then that's not going to be what you act on.

So you have to match up those two things where the threats exist and where the opportunities to have an impact exist, and then recommend the resources be devoted where you're going to get the best return on that commitment of resources. So I think there are kind of two tasks there.

DR. BRECHER: So what would be the--we're advising the government what would be the best recommendation we could have to try to match those two things? How should they look at the bigger picture and make their choices? Can we make a recommendation that would help the government make those choices?

DR. PENNER: The Committee really is in the position, as advisory, to be able to create or push an agenda, to a certain extent, as we see a safety problem

developing. Although one has to be practical, as Jay is saying, in what one is able to do, if you sit back and just wait for opportunities, then you're not allowing yourself to make those opportunities. In other words, I think we have to be able to be practice on areas where the Committee feels there is a necessity and push or urge the government to respond to those needs.

So I don't think--it's obviously a balance--but I don't think we ought to downplay the fact that this is the Committee that should be recognizing the threats and then trying to urge on any activities, whether it's practical or not, recognizing that we're trying to defend the public on some of these matters.

DR. BRECHER: Mike?

DR. DAVEY: Well, I'm not sure I quite agree, John, that our role is to identify, if I'm capturing what you said correctly, to when we identify a threat or a potential threat, that it's our job to do whatever is possible to interdict that, if I'm capturing your thought.

I think the charge today is how can we identify and interpret those risks in the larger context of other political, financial blood-supply issues, which are often very compelling, also, but may not be as quick to grasp as the immediate concern of that particular threat that's presented to us.

I think the ethicist said something. We have to be a little careful about letting immediate concerns eclipse the bigger picture, and I think we have to be cognizant of that. I'm really not sure how to advise the Secretary on this, Mark, but somehow we have to capture the balance here.

COLONEL FITZPATRICK: I have a suggestion, and if it deems worthy, I'll put it up on the screen.

I've tried to put together the agents or processes that we've heard about the past day-and-a-half that impact primarily safety. We haven't really talked about availability a lot. We've talked primarily about safety.

My proposal would be, and as a liaison I'm not sure I can make a proposal, so one of you might have to make that, would be that you form an ad hoc subcommittee or you commission a panel of experts or you commission the IOM, but that takes a long time, to review this maybe as a genesis of a process and come back to the Committee with a recommendation of a process that identifies the agents or processes that result in errors, result in risk to patients, provide you a matrix in a way to determine the impact of those. Are you impacting quality life years of a patient? Are you impacting supply by 30 percent? What is the impact of intervening and making a

change that affects the safety of the product in regards to that agent?

If you discuss those interventions, and you discuss the weighting of the issues around them, you can come up, I think, with a prioritization that takes into context all of those real-world factors, and there's a lot of gray area there. It's not a cut-and-dried number thing. But that would give you a process to look at new agents as they come about, to look at West Niles as they come up, to look at bacterial contamination in the context of everything else that's being looked at. And then you could make a recommendation about the allocation of resources through the NIH or NHLBI or grant processes, that says to the Secretary, of the monies that are available to impact on safety, perhaps FDA should be looking at regulating this item and awarding grants in that way.

To me, that's what we have lacked over the years is the item of the day, in its context, is very important, but we don't have a process that puts it into context with everything else that's going on, like the impact of recombinant Factor VIII availability and reimbursement.

I think if there were a process you could routinely use, then you could focus your discussion, and the presentations, and the agenda on things maybe in a,

not that we haven't been productive, but maybe in a more productive manner.

DR. BRECHER: Might be able also to identify synergies; for example, bar-coding patients would impact pharmaceutical errors in the hospitals as well.

Celso?

DR. BIANCO: I want to support what Mike just said, not so much with the logistics of doing it, but with the philosophy.

What I see is that our system is driven to do things in two ways: One is by a perception from the regulators or the surveillance systems, the CDC, of something coming up, be it an anthrax incident, be it West Nile Virus, or driven by industry, technological progress, by submissions that are examined one-by-one, as they're submitted by the manufacturer, in a process that is not publicly reviewed. It's more of a technocratic process that will say the product fulfills its claims or not, and we'll get a stamp of approval.

That's actually the big difference that I see between this Committee and BPAC, the Blood Products Advisory Committee. The Blood Products Advisory Committee is looking at issues here, each one of them in depth, and asking a committee of experts about the approaches.

I think our role is more global, and that's why there's so much diversity in this Committee, and I think this was intentional, and we heard that from the assistant secretary for Health yesterday.

So I think that we have, maybe with the grid that Mike Fitzpatrick is proposing or maybe suggesting that a more sophisticated grid be created, but we have to look at how each one of those things that, when happening more or less at random, as each one of those fields move or the epidemic showed up, and how they fit together.

We heard about all of this infectious disease that we know about in the last day-and-a-half, we heard about errors that were not in the program, but still appear in all of the tables as very important in the list of priorities, and I leave this room saying, if there was a resolution that I would vote for, it would be a resolution of more focus, more resources to address bacterial contamination and errors.

I saw those as the top priorities, in my mind, not that I'm ignoring any other issues, be it Chagas, be it whatever it is, but if I had one person, one lab, one dollar, that's where I would put it, if I had to make that choice.

So I want to support Dr. Fitzpatrick's grid.

DR. HAAS: I support the idea of trying to set some general parameters, but from my very nonscientific

perspective, it seems to me that we're talking about at least two populations at work; the chronic users of blood and the less-frequent users of blood. I think we have to be careful, when we set those parameters, that we don't try and catch everybody in the same net.

DR. BRECHER: Keith?

DR. HOOTS: I was just going to support what Mike is proposing, too.

I think we've heard many times both of duality of impact. If you do one thing, it obviously has repercussions mostly on supply, but even in terms of it may be that if we successfully achieve attenuation of pathogens from some of the technologies we've heard about this morning, then we can free up resources that would have been necessary to screen or at least combine screening.

But I think trying to create a system, which is what Mike is proposing, where we can look at it reiteratively and globally, is a very good idea because otherwise I think, and I'll come back to this later on in a different discussion, we do kind of end up revisiting certain things that we thought we had maybe taken care of.

I think if we force ourselves to have a reiterative process, then we won't make that naive assumption that it's taken care of. Because, clearly,

most of these things never quite get taken care of anyway.

MR. WALSH: I would mirror what's been said about Mike's proposal and would ask that he put his draft up for us to review and wordsmith. I think it would be very helpful if we went through that process.

DR. BRECHER: Chris?

MR. HEALEY: I also agree. I'd like to see Mike's proposal. I think it's a good idea. Kind of picking up on what Rick said, depending on how ambitious the Chair wants to be, you might have kind of two subcommittees; one who would be looking at current threats to safety and the other might be looking at older practices that were aimed at safety that perhaps no longer are warranted, and those resources could be reallocated to current threats.

Is that sort of where you were going, Rick?

DR. BRECHER: It may not, and we make recommendations to the assistant secretary, and it may be that we recommend that there be subcommittees of this committee to deal with those issues or we could recommend that some other body be formed to deal with it, and maybe from within government, different agencies, CDC, FDA, NIH, et cetera.

And the fact that if we make a resolution to have a group to try and prioritize things, old or new,

doesn't mean that we can't have another resolution saying that at this current moment in time, these are the two or three biggest problems and deserve the government's focus right now.

I think we could do that, which is what I think Celso was getting at.

DR. BIANCO: Exactly. Obviously, we haven't raised all of the issues here. While Mike is putting it up, it reminds me that there was a blood banker here in the audience until late this morning, but had to leave because of an emergency in the hospital, that was saying, yes, we can talk about all of those risks, but yesterday, because I didn't have enough O negatives, I converted three recipients that were O negative with O-positive blood, and so where do I balance those things?

So it has to be a big grid. We have to include availability. We have to include a lot of issues so that we see maybe we will have a vision of where to put our resources that we don't have.

DR. BRECHER: Mike, do you want to walk us through this?

COLONEL FITZPATRICK: Sure. This is not meant to be inclusive or anything. This is just a very rough look at what we've talked about.

Over here is an agent or process, and I started out with transfusion process, the sample identification

and collection, the testing in the blood bank and the laboratory, and then the labeling, and the actual transfusion event are all processes where errors can occur, and the patient get the wrong blood.

As far as agents, not going into specific agents, but being more broad, we have bacterial, viral, parasitic, prions and then of course other.

And then across the top I tried to list the factors that affect I think the concept of prioritization. How do we determine, of those, what's the most important?

Fatalities, you know, how many deaths are caused by those things?

Chronic disease, does the patient get a chronic disease or is there an acute disease that in most patients maybe is relatively easily dealt with?

Is there a cost benefit from an intervention here? That might mean the wrong way, but quality of life years as Jim AuBuchon talked to us about. These two could be the same. They might be different. It kind of depends on how you look at those things.

Supply impact, which is extremely important, what's the impact on the blood supply? We could just ignore it.

That's supposed to be humorous.

[Laughter.]

COLONEL FITZPATRICK: This is more intervention over here. You could ignore it, you could screen through the medical history questionnaire, you could have a new test, you can inactivate it, you may be putting a new risk into the clinical or blood bank staff by one of your interventions here, you can modify the process, and then you could have a total cost over here which could come out positive or negative, depending on all of these factors, and that would result in you coming up with a prioritization. This is just the patient safety piece.

On the intervention side, things that we don't discuss here, but like Sue Stramer brought up very eloquently I think at the West Nile conference, was, yes, we think we should probably test for West Nile Virus next summer. The impact resourcewise on the collection center is immense in initiating another nucleic test under an IND. That isn't really considered in here, but that comes into the testing impact. There's a lot behind those blocks that would have to be sorted out.

And then from the donor side, although it doesn't really equate if you just look at the donor side, but there are similarities from a donor or staff impact that would prioritize, like chronic disease. If we test for Chagas, and we intervene with the donor, and we prevent them having to be treated for heart problems, there's a quality life year's impact to the donor from

what we're doing which may result in the big global picture of reduced health care costs over time, which could then offset that additional cost of what we're doing. That won't be for everything that we look at, but it needs to be factored into some.

So, for the donor staff, there are factors--and they don't apply across the board, I'm just dealing conceptually here--that could apply on the donor side of the house. So that's just the idea.

And then the recommendation or proposal would be that an ad hoc subcommittee be formed to address developing a process to identify and prioritize agents/processes that impact the safety and availability of blood products in the United States. The process would then be brought back to the committee for affirmation and recommendations for resource allocation made to accomplish the appropriate intervention.

DR. BRECHER: Comments?

DR. BIANCO: Just a second part of the process, I think that the process, the subcommittee certainly could develop that, but what I suggest is that before it brings it here, it tests it with some of the issues that, for instance, we discussed today, and this be part of the whole discussion here. Because we may have a beautiful grid, but very difficult to maybe derive one. We would like to.

COLONEL FITZPATRICK: How about the process would then be validated and brought back to the committee?

DR. BRECHER: How would you validate it?

DR. BIANCO: A more gentle word.

COLONEL FITZPATRICK: I don't have all of the answers here.

DR. BIANCO: A more gentle word. Process could be tested or applied or tried.

DR. PENNER: Just thinking in terms of the income tax returns that we are all going to be involved with shortly and how many questions you can't really answer on the forms that are out there and how misunderstood, I would prefer not to have that organized a form, but maybe more breakdown into significance, impact, in general terms, so we could compare some of the priorities, but not get so selective that we have to try to push things into a column that maybe don't quite fit.

This looks like it's very nice, but I've never been a good accountant, and I always end up owing the government more money than I say I should.

[Laughter.]

MR. WALSH: I think Mike intended this to be a conceptual presentation and that the resolution, as stated, maybe without any change or some limited modification, could be proposed, and I would assume that

we're also going to have an opportunity to make a strong statement with respect to bacterial contamination that's not impacted by this. It doesn't necessarily have to be part of or a preamble to; this is more general in bacterial contamination, right?

DR. BRECHER: Yes.

MR. WALSH: So, therefore, I would like, if you can't move it, I would like to move it, and if we want to wordsmith it, we can wordsmith it in discussion.

COLONEL FITZPATRICK: I wouldn't propose that those tables even be a part of the record, actually. That's just an illustration.

DR. BRECHER: What tables?

Jay?

DR. EPSTEIN: I think it's very helpful to have a comprehensive approach, and if we go this route, I certainly would endorse it.

I think, however, that there's another way to look at the world. We have different kinds of risk, and it may not be that we have the luxury to just choose one over the other, and what I'm thinking is that we have the major risks of blood transfusion today, and we already know what they are. It's been repeated several times. It's reflected in the fatality reports. It's bacterial contamination, hemolysis, which is mainly linked to errors, and TRALI.

So I think it's self-evident that you go where the risk is. You don't need an elaborate analysis to do that much. And I would contend that the lack of progress today is for no lack of trying, and we can talk about that. It's not that we've been unaware or that there aren't steps being taken, it's just that we haven't gotten to where we want to get to, and the question is how do we remove the barriers, and they're not the same in each case.

So I think one bin is today's leading risks ought to be today's chief concerns. It's naive to think otherwise, but then what are these other things? Well, there's the whole problem of residual risks. There are things that are very worrisome, like HIV, hepatitis C, hepatitis Bank, which have low residual risks, but where there is very clearly a public mandate to do whatever can be done; in other words, do the right thing, do the best you can.

This comes back to the whole tension between what's good for the many and what's good for the individual. There's no question that there's been a very loud voice of the individual expressed through the political process. Individuals don't want to have an HIV or hepatitis risk from their blood products.

So I think we simply have to accept the fact that it's part of the political landscape to continue to

be aggressive and do whatever we can about these known risks, for which we have effective interventions, but for which residual risk remains. And I think that if you put those on this chart, they fall to the bottom, but what good does that do you? So I would contend that they are simply another bin.

And then I think that there's a third category all together, which is unquantified risks, where we either know there's some risk, but we don't know how big it is, or we're not sure there's risk at all, but if it's real, it's very worrisome. There's sort of a whole bunch of things that live there. We have West Nile Virus. It happened last year; you know, the biggest reported human outbreak. A small number of documented transfusions has raised an acute concern that we need to keep that from happening again, if we possibly can. That's legitimate, but let's face it, we don't really know how big that risk is going to be in '03 or '04 or '05.

Worse yet, you have vCJD, where we don't even know if the transfusion risk is real, although the preponderance of the experimental data, mainly in animals, suggest to us that it might well be, but how big is it? Well, it might be real. It might be real, but small.

So we have these fearful things, and then you have Chagas disease, where we know it's transmissible, we know it causes very bad chronic disease, it's untreatable, and yet the magnitude of the problem is unknown.

So I just think that, whereas, it's useful to have a grid, and where it's useful to understand how any of these issues fit along a common continuum of considerations, I think that, you know, considerations of the real world would suggest to us that there are, nonetheless, some discrete areas of concern, where we're just not in a position to trade one against another, I see it more as prioritizing within certain categories. How should we prioritize our effort for the known risks that are not currently well addressed? How should we prioritize our efforts for the residual risks that, albeit small, remain of intense public concern? And how should we prioritize our efforts to address the unquantifiable risks that we do face, some of which we know are real and some of which are theoretical?

I just think that that gets us a little closer to a framework for real-world decisionmaking rather than an abstract ranking.

DR. BRECHER: Celso?

DR. BIANCO: Jay, you said it very well, and I think that the system, as refined, could certainly and

should certainly take those into account. And, actually, even if the presentation by Jim AuBuchon was very ranking, I think his first slide, what was the public concern, HIV, HIV, HIV, HIV. And I think that you reflected on that very well.

However, when we talk about prioritizing, the way we work and the constraints of the real world outside that we have a definite pot of money, that that pot of money is not going to change. There is that money, resources. And so we are trying to choose between the least and the most dangerous. And I don't think that's how--I think that this committee can recommend that more resources or more efforts should be applied to different sectors of something that is very high in the minds of the public, consequently very high in the minds of our political world in Congress, and hopefully very high in the minds of HHS.

And I think that our role is to raise our awareness to the issues in each one of the three bins that you have that deserve attention and for which we can request more resources, even if we don't get them.

DR. BRECHER: Rick?

DR. DAVEY: Yes, I agree with Celso, and also, Jay, I think you captured some very important information.

I think I'd like to look at the grid, though, as providing more or less a platform or a basic structure of information that can always be attended to, no matter what the question is. The political and the societal pressures will certainly come out, but our grid gives us the discipline to make sure we address all of those issues in whatever the committee decides. So I think it does give us a context of the broad picture for us to assess the immediate concerns. So, Mike, I certainly support it and support your suggestion of a subcommittee to look at it.

DR. PENNER: I think we have a very representative group in this committee, and so we have opportunities to bring all of the information and concerns and interests up, I think more appropriately than perhaps in the public. We have a chairman who can canvass the group. We have some reliance on his ability to juggle what is permissible and what he knows is going on governmentally as well as the insistence of the group of where the problems are, should be able to come up with, I think, an agenda or program that at least we could follow.

I think I would feel comfortable in leaving it up to the chairman to utilize us appropriately for this program. If you want to have a subcommittee to do it, that's fine as well. But I think we have a committee.

DR. BRECHER: Yes?

MR. ALLEN: I just wanted to pick up on some things that Jay had mentioned in terms of how I see things and our obligation here to people in this country. And I think it's kind of ironic to be in D.C. when you hear every day about the new incidence and new HIV infection in this city alone and how astronomically high it is versus other parts of the country. And I have to remind myself of how naive I was when I came to this committee, and I have to accept that I learned a lot. I think I learned more from the people I disagreed with than I ever thought possible.

But, you know, there's a segment of this country that is in itself isolated and feels isolated from the rest of this country, and I don't mean just minorities for the fact of your color, but I mean there's parts of this country that feel isolated. And my community as an example--and I'm going to use these names because I don't think they're going to mind me using their names. But my community needs to know about the Dana Kuhns, the John Walshes, and the Cory Dubins of this world. They need to know that these people exist and what they've gone through. They also need to know that they're not merely just surviving, but they're fighting.

So, you know, when I hear what we're trying to move this committee to do for people of this country and

understand there's a much bigger picture than just a few people in mind, but, you know, a lot of parts of this--a lot of people in this country don't believe that this government sees them or cares about them. And I just believe personally that we have an obligation to make sure that they understand that we're there, that we do care. And I just don't want that to be forgotten. I don't want those people to, once again, feel forgotten in all of the terminology and science of this committee and other committees. I just think that that's something that needs to be recognized by this committee again so that we don't repeat some of the mistakes we've repeated in the past and that we learn from them and learn to cooperate a bit better so we can move on and do more for more people than just a few.

DR. BRECHER: Mike?

COLONEL FITZPATRICK: Yes, I see this as just a tool for the committee. I don't see it as supplanting anything in the discussion or the agenda. I just see it as a tool to help the committee make reasonable decisions, taking into account all those other things like the resurgence of HIV, like the alpha 1-antitrypsin group who needs a voice, that there are many facets to this committee that they have to make decisions about. And if we can come up with a tool that maybe would even reduce discussion about some things and allow them to

discuss other important elements that they can use, that it might be beneficial.

DR. KUHN: I would like to just embrace what Jay was saying about trying to--and maybe even try to figure out how to incorporate it into what Mike has put up there about the known risks, the residual risks, and the unquantified risks, and to kind of--because this meeting has opened my eyes to the fatalities that are out there, that now in comparison with what's happening with HIV and hepatitis C, there are other concerns out there I think we really need to address on behalf of the citizens of the United States.

I think that the public eye is expecting us, in all areas, not just HIV and not just in hepatitis, to seek a zero risk or as close to a zero risk as we possibly can get. And I think these other areas have been neglected because of the public opinion and public push, which has in its own way been right where they have been doing this in order to get us to where we are now. But I think now it's time to take a serious look and to try to embrace these, what I consider are the priorities, not in any particular order, but the unknown risks, the residual risks, and the unquantified risks. And if there was a way to incorporate it into this statement, I think it would be very acceptable.

DR. GOMPERTS: Jay's characterizing the various facets of the problems that we have to deal with is obviously useful. But, in my opinion, it's a great place to start because in each of these buckets, technology is moving. New agents become a potential threat. The vaccinia situation is a new one that we'll have to deal with. But ultimately the key is: What is it that this committee can actually contribute to these things, to these three broad buckets: the changing scenario--and we've revisited a number of these technologies and these problems on a number of occasions over the years.

So what can this committee do about it? How can we facilitate and advance, societal advance, governmental advance, in dealing with these issues? I think that really is at the core of it.

MS. PAHUJA: I feel like there's a tool or a priority that we haven't really mentioned, which is sort of outside the list of disease threats, which is really the public education component, which sort of speaks to what Dr. Bianco was talking about with sort of the public's perceived risk of greatest threat and what the experts feel the actual threats are. We need to resolve that somehow, make some sort of recommendations towards if, in fact, there are other concerns out there, which there are as we've learned the last two days, how do we tell the public about what those concerns are without

forgetting that we still have obligations for other threats that we've dealt with in the past?

I definitely feel like that public component is a priority. After all, while there are experts and there are consumers, to some extent we're all consumers of this system. Potentially we all could be. And how--whether we for ourselves or our loved ones perceive the product we're receiving, it's a very important aspect. And I think when you do a better job of advising the Secretary in terms of including that component in every action that's made so there is some sort of trust.

DR. CHAMBERLAND: In listening to the discussion, I think at least how I'm sort of seeing it span a spectrum of the outcome recommendation, if you will, from the committee, at one end of the spectrum is something more what I'll call qualitative or descriptive, sort of along the lines what Jay articulated, you know, broad brush strokes. You know, I don't at all disagree with what Jay said in terms of where the data that we have at the moment is driving us towards these big three, but the important other categories.

At the other end of the spectrum, at least the way I'm seeing Mike's grid up here, is a much more rigorous, quantitative approach that--or it could turn into that, that kind of an exercise, which really strikes me as the stuff of GAO reports or Institute of Medicine

reports that, you know, really require a lot of time and heavy commitment of resources.

And I guess I--at least I wasn't sure what the outcome of the last two days meeting was supposed to be, whether it was just sort of some general broad brush strokes--I guess I didn't think it was a proposal that we on our own or that we propose to the Secretary's office that they put into place some mechanism to develop a national research agenda or a national action plan, if you will, something like that for blood safety-related research.

So I guess to me that's sort of the first cut, which direction do we want to go in, and then I very much agree with what Ed just said. Practically speaking, what is it that this committee can contribute or facilitate? I mean, others have said this. You know, we heard a lot of presentations. So it's not like it's a big secret what the biggest issues, unresolved issues are at the moment. But what is it that we're going to--how can we make a difference? Because we know that there hasn't been a lot of progress, or as Jay said, they just haven't been well addressed. And I think that inevitably that gets tied to resources.

DR. BRECHER: Let me give you some background as to why I chose to push the agenda in this direction. There are those of us in the field who recognize that

what the greatest risk is is often not perceived by the general population. And I think we've made a good point of putting that out on the table.

But there has also been a frustration that the greatest risk has not received appropriate emphasis within the government. And what I think might come of this--and I'm trying not to push the committee too far in one direction or another, because clearly I have my own soapbox--is that there are certain diseases or processes that the government has said we think this is very important, we're going to put a lot of resources behind it. And the question I think for the committee is: Were those well chosen? Or should there be another mechanism to help steer the government to where they should spend their dollars?

So we could just--we could do nothing and pack up and go home, or we can say that given what was presented, we think that these are the major problems that are facing transfusion medicine today and require emphasis, similar to what Celso suggested. We could suggest that there be a systematic look at risks, whether that be a subcommittee or the IOM or something like that.

But I think we need some resolution that comes out of this committee one way or the other, and we have a lot of smart people at this table, and I'll leave it to you guys to make suggestions.

Chris?

MR. HEALEY: I think Colonel Fitzpatrick has kind of amended his language up there to reflect what Dr. Epstein was saying. I think it captures that nicely. I wondered if that's a platform we could start from if we're looking for a work product for the end of the day.

DR. BRECHER: I still struggle with how you're going to test it. I'd rather not put something on paper unless I know how we're going to do it.

DR. DAVEY: It looks to me, Mark, that the resolution as worded does give the subcommittee some latitude to draw on the committee's discussion, which is very valuable, and this grid and to develop a schema that they can then reflect back to us. So I would support giving Mark the go-ahead with the subcommittee and with some fair latitude to develop a process that can be sent to us for further review, something along the lines of this grid, though.

DR. BRECHER: Okay. So it sounds like that's a motion. Do we have a second for the motion? Keith?

DR. HOOTS: Second.

DR. BRECHER: All right. All those voting members who would be in favor of the wording as illustrated on the screen here, all in favor?

Okay. All those opposed?

I get 12. It's 12-0 in favor of this motion.

DR. HAAS: Mark, I think it's important--and Mike--I'm forgetting names--in his description that this is a tool that sets a framework. I think there's always when you get a tool the tendency to say, oh, we put in the numbers or the words and whatever comes out the other end is the answer. And I don't think that's the intent, and I think it ought to be clear that that's not the intent.

DR. PENNER: I don't think we've included a grid, though.

DR. HAAS: No. No, the grid--

DR. PENNER: This is--the grid is--

DR. HAAS: --is not going to be there, right.

DR. PENNER: Keep the grid out of it. Just remember the elephant that was created by the committee.

MR. WALSH: Mr. Chairman, I also think we need to try to craft some language--where's Jay Epstein when we need him?--craft some language with respect to a focus on bacterial contamination. I mean, it's very clear--I think everybody that has said anything the last hour has specifically referenced that this needs to--that this is a priority and that somehow this is one of the reactions to--not somehow. This is a reaction to setting up a process to look at all of those potential risks in the future. But right now, how do we emphasize to the Secretary, Assistant Secretary, that this committee

realizes that bacterial contamination is an issue that needs to be addressed. You know, I'm a little brain-dead at this stage of the day, but I think we need some good language to embrace that.

DR. BRECHER: Celso?

DR. BIANCO: I think you've said the good language, but I think it should be a separate motion.

MR. WALSH: I agree. That's what I'm suggesting.

DR. BRECHER: Okay. Why don't we--do we hear a separate motion? Do you want me to paraphrase back what you just said?

MR. WALSH: If you would, Mr. Chairman. Thank you. I should have just written it down.

DR. BRECHER: The committee recognizes that bacterial contamination of--shall we say "platelets," narrow it, instead of "blood products"?--platelets is the greatest risk of transfusion-transmitted disease and requires emphasis in future research and regulatory--something. Jay, help me here.

DR. EPSTEIN: It troubles me, Mark. I know that it's the leading infectious cause, but numerically it's not really a bigger cause than hemolysis.

DR. BRECHER: Well, maybe we can just say the top three.

DR. EPSTEIN: Yes, that's how I see it.

DR. BRECHER: Okay. We can certainly do that. I think that would--so that the committee recognizes that the top three causes of fatalities today are bacterial contamination of platelets--I'm going to do this in alphabetical order--hemolysis due to errors, and transfusion-related acute lung injury. I hope someone's writing this down.

Okay. The committee recognizes--maybe I should just go back.

[Pause.]

DR. BRECHER: Jay, help me with the last couple words here.

[Pause.]

CAPTAIN McMURTRY: Mark?

DR. BRECHER: Yes?

CAPTAIN McMURTRY: You're the chairman, but why don't you let everybody have a break for a second while we craft these--

DR. BRECHER: Okay. We'll take a ten-minute break.

[Recess.]

DR. BRECHER: Everyone take their seats, and we can look over this wording. What we've done is we've combined the two proposals. Let me just read through it from the top:

The committee recognizes that the current leading causes of transfusion-related fatalities are: A, bacterial contamination of platelets; hemolysis due to errors; and transfusion-related acute lung injury, TRALI. And that efforts to address these threats have been limited in comparison to other threats. The committee further recognizes that public attention remains highly focused on residual risks from HIV and hepatitis agents, and on less quantifiable, known, and theoretical risks. The committee also finds that technologies already exist that could effectively reduce the risk from bacterial contamination and hemolysis.

Therefore, we recommend that: one, the Secretary take steps to facilitate implementation of available measures that could reduce the risk of bacterial contamination and hemolysis; two, an ad hoc subcommittee be formed to identify and evaluate residual, known, and unknown risks affecting blood safety and supply, both in relation to etiologic agents and the processes used in transfusion medicine. The subcommittee shall be tasked to propose prioritization of efforts to address these risks for further consideration by the committee.

Jeanne?

DR. LINDEN: Talking about risks affecting supply seems a little broad. Can you clarify what's meant there?

DR. BRECHER: Well, I think, you know, anytime we're talking about changing a process, we may take out a subpopulation of donors, and that would affect supply. So that has to be weighed into any change that we might want to enact.

DR. LINDEN: But only as part of the issues related to blood safety, not broadly supply issues in general, which are much more larger in scope.

DR. BRECHER: Jay?

DR. EPSTEIN: Would it help to have the word "secondarily"? In other words, risks affecting blood safety and, secondarily, supply? It's really the interventions that affect supply, right?

DR. BRECHER: Okay. Are there--

MR. WALSH: Or we could use "availability."

DR. BRECHER: Secondarily, availability, rather than supply? What's the committee's choice, supply or--okay. Availability it is.

DR. PENNER: On number one, how about assist and support measures to investigate further the relationship--or investigate further--let's say--I'm trying to think of getting that in for some of the testing program that you had considered, not just implementation but--

DR. BRECHER: Well, and optimize supply, reduce the risk and--

DR. PENNER: Well, for the infectious--for the bacterial contamination, and, let's see, two, investigate--interventions that would--that could be applied to correcting this condition, something in that order. Because you need really some support there to promote some of the studies that have been mentioned previously to come up with some reasonable recommendations.

DR. BRECHER: And we could say, where possible, you know, at minimal cost or--

DR. PENNER: I wouldn't put cost in it because we can get--because you really want to encourage the process, and it doesn't make any difference whether it comes entirely from government or it may be private sources or blood banking communities may wish to get involved. But that has to be promoted. You want to support it.

DR. BRECHER: Well, and possibly improve the storage of blood products.

DR. PENNER: To improve the storage of blood products.

MR. HEALEY: Mark, does that first point presuppose that the available measures are demonstrated adequate to address bacterial contamination?

DR. BRECHER: No, it does not presuppose. We realize there are technologies that, in all likelihood, would impact both in terms of bacteria and when we're talking about hemolysis we're mainly talking about bar coding patient samples, et cetera, throughout the hospital, which would also carry over into the pharmacies.

Jeanne?

DR. LINDEN: Along that line, what's conspicuously absent is the idea of promoting the development of additional technologies, because all we're saying is the ones that are already out there, we should try to facilitate, but we're not saying anything about trying to develop new ones. Is that intentional?

DR. BRECHER: Jay?

DR. EPSTEIN: Well, I think my concept on this is that the thing that distinguishes bacterial contamination and hemolysis is that there are things we could do now that we're not doing now; therefore, there's a stand-alone point to be made about those.

Now, in the second point or candidate third point, I think something useful can and should be said about supporting developmental--you know, development of other interventions. I would certainly agree with that. But I think there is a stand-alone point about, you know,

hemolysis and bacterial contamination. We could do things today that we are not doing.

DR. BRECHER: So do we want a separate point about developmental? Is that what I'm hearing? Jay?

DR. EPSTEIN: I think it either comes in two or it becomes a point three. Because you're not going to do that apart from a general consideration of, you know, where are the risks and what are the opportunities.

DR. BRECHER: Okay. Why don't we make it number three.

MR. HEALEY: Jay, was your point that it could be subsumed under point two that's already there?

DR. EPSTEIN: Well, I think we could add a second sentence that charges the subgroup additionally to examine potentially fruitful areas of research or product development to address these risks.

DR. BRECHER: So what is--is that agreeable, everybody, that wording?

CAPTAIN SNYDER: Jay, do you want the subcommittee to do that, or do you want the department to do that?

DR. EPSTEIN: Are we ready to task the department? See, the problem with two is we haven't set priorities yet, so if you call for, you know, more funds for development, to develop what? So, I mean, you know, we each have our own list actually jotted down about a

dozen things I'd like to see happen. But as a committee, we haven't decided what they are yet.

DR. BRECHER: I think if the subcommittee is tasked to prioritize things, it's implied that once we prioritize, that action will be taken on those. That's our intention, I think.

DR. BIANCO: Actually, right after to propose prioritization of efforts, it could be by government, industry, and health care system.

DR. BRECHER: Government, industry, and the health care system?

DR. BIANCO: No?

[Pause.]

DR. BIANCO: So it's broader. It's not just the committee doing the work, but it involved--it's global.

DR. PENNER: On the first one, do you want to take out "to possibly," just put "and improve the storage of blood components"? You don't want to waffle.

DR. BRECHER: Jay?

DR. EPSTEIN: John, I'd like to hear a little discussion about what you're intending there. Is that focused just on the issue of platelets? Are you talking about, you know, fresh or frozen red cells? Are you talking about lyophilized platelets? I mean, what are we really talking about there? And how does it directly link to bacterial contamination and hemolysis? In other

words, what's the lead threat that you're trying to fix with storage?

DR. PENNER: Okay, two things. If one is on platelets, and then, secondly, it is by--we need some support for investigation of this area, which we have not had and, as you've already heard, we've had problems because of the costs, some of the cost factors in getting this done. How do we get that into the message? Because it relates specifically to the bacterial contamination problems in platelets.

DR. BRECHER: Yes, I narrowed it to just platelets because that's how the sentence was beginning.

DR. PENNER: Yes, I think that's reasonably.

DR. BRECHER: Yes, Mary?

DR. CHAMBERLAND: Along the same lines, could I hear some additional discussion about what the committee--I mean, the literal interpretation of this, the Secretary facilitating implementation of available measures to reduce bacterial contamination and hemolysis, can I hear some sense or some discussion about the practical interpretation of this? What are we asking the department to facilitate? Facilitate research dollars? Facilitate FDA guidance to mandate some of these? I'm just not--I guess I want to have a better sense of what the intent is behind this first--

DR. BIANCO: We are avoiding the magic word here, that is, the resources. I think that we all heard that the reason why there hasn't been sufficient investment or there is even resistance to follow the protocol that Jay was proposing to confirm or to license a bacterial detection system is the number of cultures necessary and the added cost to the blood product that the system doesn't want to accept?

DR. BRECHER: Jay?

DR. EPSTEIN: Well, we could be overt and say that the Secretary commit resources to facilitate implementation.

DR. CHAMBERLAND: But committing resources to facilitate implementation, again, a literal interpretation means doling out dollars to blood collection agencies and hospital transfusion services to pay for the equipment and the personnel and the space that's needed to buy this equipment for bacterial contamination--I don't think that's what you mean but--

DR. BRECHER: No, that's not going to happen.

DR. CHAMBERLAND: Right.

DR. BRECHER: I think we're looking at guidances, expedited reviews, things like that. I think that is where we're headed.

DR. CHAMBERLAND: I don't think it's what you want, but I'm concerned that that language--

DR. DAVEY: Could you just say facilitate efforts to reduce the risk?

DR. BRECHER: Well, I think the available measures was put in there specifically because there are technologies for these two, and we stated that above. So I think Jay is right that those words need to be there.

[Pause.]

DR. BRECHER: Well, we're open to other wording suggestions instead of facilitate implementation. I think this--

DR. BIANCO: What if we say, instead of facilitate because that's kind of loose, expedite?

DR. BRECHER: Is that okay with the committee, expedite?

DR. BIANCO: Mary has another suggestion.

DR. CHAMBERLAND: Again, I'm just being difficult. Can the people that made this proposal, can you tell me what it is you want the department to do? And then maybe we can find the language. But what are some parenthetical examples that you want the department to do?

DR. BRECHER: Jay?

DR. EPSTEIN: All right. Some of the things that I think are the tasks would be funding or finding ways to orchestrate funding of multicenter studies to validate culture as a pre-release test; funding or

finding ways to promote funding of studies to validate seven-day platelet shelf life; funding or finding ways to fund efforts to implement error trapping and correction mechanisms applicable to the donor identification, the sample integrity, the database management of the cross-match, et cetera.

So it's those actions that would move us from having a technology on a shelf to having a technology with the proven benefits, which is then implemented.

DR. CHAMBERLAND: So it's really identification of resources that can be directed to support research for--

DR. EPSTEIN: It's not solely research. See, I think the distinction that we're getting at here is that some of the answers are known. We know we could use culture. The question is how do we do it. We know we could use data automation, things like blood lock or--I forget what it's called--the donor ID.

DR. BRECHER: Right, bar-coded identification.

DR. EPSTEIN: Right, bar codes, you know, reducing the number of manual steps, et cetera. I mean, we know there are things we could do, and what's not entirely known, you know, to me or necessarily all members of the group, is what the barriers really are. Or as you walk into the hospital, what's the problem today? It's like Celso's question: Why don't we have

the automation? You know, why don't we have the hard-wired systems that prevent the unit and donor mismatch? The technologies are there. So what we're looking for in a general way is the resources to overcome those obstacles.

Now, some of those obstacles lie in the research domain, but some don't.

DR. PENNER: Mark, I think you've got a general consensus, but the wording needs a little work, which can be transmitted to all of us to sign off on, whenever you feel comfortable you've got it down.

DR. BRECHER: I think the hour is growing late. Is everyone comfortable with that? We'll tweak in a few examples, e.g.'s. We'll pull those from the minutes, from some of the things that Jay said, and we'll circulate that for final approval. If everyone--let's see. All who are in favor of that motion? Eleven in favor.

All opposed? Zero. Okay.

Any abstentions? I abstain as Chair.

All right. Then this concludes this meeting of the Advisory Committee. Thank you all.

[Whereupon, at 4:00 p.m., the meeting was adjourned.]